Response to FDA Request for Information on Talc
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Article

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Safety Assessment of Talc as Used in Cosmetics

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Abstract

The Cosmetic Ingredient Review Expert Panel (Panel) assessed the safety of talc for use in cosmetics. The safety of talc has been the subject of much debate through the years, partly because the relationship between talc and asbestos is commonly misunderstood. Industry specifications state that cosmetic-grade talc must contain no detectable fibrous, asbestos minerals. Therefore, the large amount of available animal and clinical data the Panel relied on in assessing the safety of talc only included those studies on talc that did not contain asbestos. The Panel concluded that talc is safe for use in cosmetics in the present practices of use and concentration (some cosmetic products are entirely composed of talc). Talc should not be applied to the skin when the epidermal barrier is missing or significantly disrupted.

Keywords

talc, safety, cosmetics

Introduction

This assessment presents information relevant to the safety of talc as used in cosmetic formulations. Reported functions of talc in cosmetics include abrasive, absorbent, anticaking agent, bulking agent, opacifying agent, skin protectant, and slip modifier.[1] The noncosmetic issue of the prohibition of the use of talc in medical examination gloves[2] will not be addressed in this safety assessment.

In 1976, specifications for cosmetic talc requiring that no detectable fibrous, asbestos mineral be present were developed.[3] Therefore, this report will only address the safety of talc that does not contain asbestos. Because the specification was developed in 1976, that year was used in determining what data are more likely relevant to the safety of cosmetic talc; therefore some studies performed prior to 1976 may not be relevant to talc as currently used in cosmetics, and they might not be included in this assessment.

Reviews and responses specific to the National Toxicology Program (NTP) study are included in the section on Carcinogenicity. The following are conclusions from various workshops and review articles on talc:

- In 1978, the Public Citizen Health Research Group contacted the US Food and Drug Administration (FDA) with a letter stating their concern that talc is possibly carcinogenic and that the FDA should eliminate the use of talc in drugs and cosmetics even if the results are not conclusive.[4] The FDA responded that it was studying talc and believed that any risk from talc was related to contamination by asbestos.[5]
- In 1983, the FDA received a citizen's petition requesting that cosmetic talc be labeled with an asbestos warning statement, information on asbestos particle size, and the proportion of impurities in the product.[6] The FDA denied this request, stating that "there is no basis at this time for the agency to conclude that this is a health hazard attributable to asbestos in cosmetic talc. Without evidence of such a hazard, the agency concludes there is no need to require a warning label on cosmetic talc."
- In 1992, the Environmental Protection Agency (EPA) issued a "Health Assessment Document for Talc."[7] The review concluded that talc is not carcinogenic following inhalation exposure or intraperitoneal (ip), intrapleural, or intrabursal administration to rats, hamsters, and mice.

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However, these studies were not considered fully adequate to evaluate the carcinogenic potential of talc. The review noted that evidence from 2 studies suggests that talc may be an effective cocarcinogen when administered intratracheally with benzo[a]pyrene (B[a]P) to hamsters.[8,9] The Cosmetic Ingredient Review (CIR) Expert Panel determined that the results of these studies were not relevant to the cosmetic use of talc and that the study was not well-designed to study talc.

- In 1993, the NTP issued a report, "Toxicology and Carcinogenesis Studies of Talc (CAS No. 14807-96-6) in F344/N Rats and $B6C3F_1$ Mice (Inhalation Studies)," that concluded there was *some evidence of carcinogenic activity* in male F344 rats, *clear evidence of carcinogenic activity* in female F344/N rats, and *no evidence of carcinogenic activity* in male or female $B6C3F_1$ mice exposed to aerosols of 6 or 18 mg/m^3 nonasbestiform cosmetic-grade talc in a lifetime study.[10] (This study and responses to the report will be described in detail later in this report).
- In 1994, a public workshop titled "Talc: Consumer Uses and Health Perspectives" was organized under joint sponsorship of the FDA; the Cosmetics, Toiletry, and Fragrance Association (CTFA, now known as the Personal Care Products Council [the Council]); and the International Society of Regulatory Toxicology and Pharmacology (ISRTP).[11,12] The purpose of the workshop was to provide a forum for an updated discussion of the origins, manufacture, characterization, toxicology, and epidemiology of talc and related products. The principal focus was the then-latest toxicological and epidemiological studies as they related to the safe uses of talc in cosmetic products. The characteristics of cosmetic-grade talc, the history of talc use, and quality-control measures for talc were discussed, as was an appraisal of the NTP inhalation study on talc. The regulatory history of talc was also reviewed. The workshop concluded that the NTP bioassay results could not be considered a relevant predictor of human risk, and in regard to proposed association of talc exposure and ovarian cancer, the workshop Panel found that the epidemiological data were conflicting and remain equivocal.
- In 1994, the Cancer Prevention Coalition (CPC) submitted a citizen petition to the FDA seeking labeling on all cosmetic talc products.[13] The requested labeling was a warning that talcum powder causes cancer in laboratory animals; frequent talc application in the female genital area increases the risk of ovarian cancer. This petition was denied.[14]
- In 2000, talc was nominated for review in the NTP 10th Report on Carcinogens because the NTP bioassay reported clear evidence of carcinogenic activity of talc (nonasbestiform) based on increased incidences of alveolar/bronchiolar adenomas and carcinomas of the lung in female rats and because published epidemiology studies suggested that talc exposure was associated with lung cancer in pottery workers and ovarian neoplasms in women. (65 FR 17891)[15] However, the NTP deferred consideration of listing talc (cosmetic and occupational exposure; both asbestiform and nonasbestiform) as a carcinogen because of considerable confusion over the mineral nature and consequences of exposure to talc (70 FR 60548),[16] and in 2005, talc was withdrawn from review.[17]
- In 2008, the CPC again submitted a petition to FDA seeking labeling on all cosmetic talc products.[14] The requested labeling was a warning that frequent application of talcum powder in the female genital area substantially increases the risk of ovarian cancer. It does not appear that FDA has responded to this petition.
- In 2010, the International Agency for Research on Cancer (IARC) Working Group published that there is *limited evidence* in experimental animals for the carcinogenicity of talc not containing asbestos or asbestiform fibers.[18] The Working Group reviewed studies in which talcs of different grades were tested for carcinogenicity in mice by inhalation exposure or intrathoracic, ip, or subcutaneous (sc) injection; in rats by inhalation exposure or intrathoracic or ip injection, oral administration, or intrapleural or ovarian implantation; and in hamsters by inhalation exposure or intratracheal injection.

For humans, the determination of the IARC Working Group was that perineal use of talc-based body powder is *possibly carcinogenic to humans (Group 2B)*, and that inhaled talc not containing asbestos or asbestiform fibers is *not classifiable as to its carcinogenicity (Group 3)*.[18] In evaluating the carcinogenicity of talc in humans, the working group reviewed cohort studies of talc miners and millers; cohort and case-controlled studies examining the association of cosmetic talc use and the risk of ovarian cancer in humans; and the animal data and evidence regarding the potential mechanisms through which talc might cause cancer in humans. The working group found there is *inadequate evidence* in humans for the carcinogenicity of inhaled talc not containing asbestos or asbestiform fibers, and there is *limited evidence* in humans for the carcinogenicity of perineal use of talc-based body powder.

Many occupational exposure studies are available that describe the effects reported in talc workers. Although the occupational exposure to talc is not at all similar to the cosmetic exposure to talc, these reports are summarized in this safety assessment to provide a total overview of available information. Occupational studies in which talc was known to contain asbestos are not included.

Mineralogy and Chemistry

Definition and Structure

The term talc has 2 meanings: (1) as a mineral, the talc corresponding to the chemical formula of hydrous magnesium

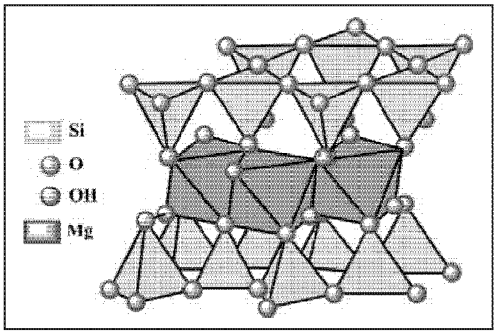

Figure 1. Schematic structure of talc.[27]

silicate and (2) commercially, as a product that can be used industrially in pharmaceuticals and cosmetics.[19] The mineral talc has the formula $Mg_3Si_4O_{10}(OH)_2$ and[20] a theoretical chemical composition, expressed as oxides, of 31.7% by weight (wt) magnesium oxide (MgO), 63.5% silicon dioxide (SiO_2), and 4.8% water (H_2O).[21] As a cosmetic ingredient, talc (CAS No. 14807-96-6) is defined as a powdered native hydrous magnesium silicate, sometimes containing a small portion of aluminum silicate.[1]

Talc belongs to the silicate subclass phyllosilicates[22] and is a sheet silicate. The structural unit consists of 3 sheets, that is, octahedrally coordinated magnesium hydroxide groups (brucite layer) sandwiched between 2 layers of tetrahedrally linked silica layers.[23,24] The apical oxygen atom positions of the tetrahedral layers are shared with one of the oxygen atom positions of the octahedral layer.[25] The composite sheets repeat every 9.4 Å. Stacks of the triple-sheet crystalline units are held together by van der Waals forces[26] (Figure[27] 1).

Small amounts of aluminum and iron(III) can substitute for silicon in tetrahedral sites.[21] Trace amounts of nickel and small to moderate amounts of iron(II), iron(III), aluminum, and/or manganese can substitute for magnesium in octahedral sites. Such substitutions are bound within the crystal lattice and therefore do not exert any biological action. The replacement of hydroxyl groups by fluorine may also occur.

The relationship between talc and asbestos is commonly misunderstood.[26] The presumption that asbestos and talc are commonly associated, or comined, is incorrect. Talc and asbestos (or even asbestiform materials; asbestiform refers to a crystallization product of a mineral in which the crystals are thin, hair-like fibers with enhanced strength, flexibility, and durability[28]) form under different geological conditions and are separated into adjacent, but disparate, strata. Accordingly, by utilizing proper mining methodologies, asbestos contamination is avoided. Moreover, the absence of asbestos in talc is routinely confirmed in ore samples through a battery of analytical techniques.

Physical and Chemical Properties

The mineral talc has a predominantly plate-like structure, with adjacent layers very weakly bonded by Van der Waals forces.[21] This allows talc to be easily sheared along the plane, giving it its natural slippery feel as well as its softness. Talc is the softest mineral, with a hardness of 1 Mohs (scale of 1-10).

The physical form of talc rock is related to the source and geological conditions that exist during formation of the deposit.[21] The platelet size of talc determines its lamellarity, which, in turn, is related to the genesis of talc deposits. Highly lamellar talc (informally classified as macrocrystalline talc) has large individual platelets, whereas microcrystalline talc has small, randomly oriented platelets. The size of an individual talc platelet can vary from 1 μm to over 100 μm, depending on the formation of the deposit.[29]

The particle size of talc powder depends on the process used to make the powder.[21] Typical cosmetic talcs have average particle sizes ranging between 4 and 15 μm when measured by sedimentation methods, with only minor fractions consisting of particles considered respirable. Another source recites that the "fineness" of talc used, characterized as 200, 325, or 400 mesh (ie, particle size distribution that allows 95% to 99% of the product to pass through a 200, 325, or 400 mesh, respectively [74, 44, or 37 μm, respectively], when wetted out with alcohol and dispersed in water) depends on the use in cosmetics.[26] For example, 200-mesh talc is preferred for body powders, while 400-mesh talc might be used for pressed powders. The cosmetic ingredient specifications for talc state that in a screen test, 100% passes through 100 mesh, 98% minimum passes through 200 mesh, and finer grades are as specified by the buyer.[30] Physical and chemical properties of talc are summarized in Table 1.

Analytical Methods

According to CTFA test method J 4-1, the absence of asbestiform amphibole minerals in cosmetic talc is determined using the generally accepted method of X-ray diffraction and optical microscopy with dispersion staining.[31] Other methods for the detection of fibrous amphibole, such as transmission electron microscopy (TEM) with selected area diffraction and electron microprobe, were considered but were not adopted by the cosmetics industry trade association when the testing methods were first published because of the drawbacks associated with those methods, that is, the amount of the material examined is small; the expertise required; and the expense of the equipment. However, electron microscopy, including TEM and scanning electron microscopy, are now routinely used as supplemental and complementary methods of X-ray diffraction and optical microscopy.[32] Infrared spectroscopy, which permits detection at a 0.1% (w/w) minimum detection level, also can be used to identify asbestos in talc.[21]

Free crystalline silica (quartz) in talc can be detected using differential thermal analysis, which permits detection at a 0.5 to 1.0% (w/w) minimum detectable level (CTFA test method J 5-1)[33] or by X-ray diffraction (CTFA test method J 6-1).[34]

Table 1. Physical and Chemical Properties.

Property	Description	Reference
Physical appearance	Essentially white, odorless, fine powder	30
	Ranges from snow-white to black, including greenish-gray and shades of green, pink, and red	44
	White, apple-green, gray powder; pearly or greasy luster	212
Mohs' hardness	1	213
	1-1.5 (may be harder when impure)	25,212
Crystal system	Triclinic	25
Morphology	Perfect (001) cleavage	25
Melting point	900°C-1000°C	214
	1500°C	29
pH	8.8-9.5	19
	7.7 ± 0.5	45
Density	2.7 g/cm^3	215
Surface area	<20 m^2/g	216
Solubility	Insoluble in water, cold acids, or in alkalis; soluble in hot concentrated phosphoric acid	61
Optical properties		217
n_x	1.539-1.550	
n_z	1.589-1.600	
Indices of refraction	α = 1.539-1.550	18
	β = 1.589-1.594	
	γ = 1.589-1.600	

In early studies, the analytical methods used to identify the asbestos in talc were not performed and/or interpreted correctly. Misidentification of asbestos in talc can result from misinterpretation of the data obtained when performing an analytical procedure.[35]

Constituents/Impurities

Associated minerals found in commercial talc products vary from deposit to deposit depending on the conditions of formation of the deposit.[21] The most common minerals associated with talc are chlorite, magnesite, dolomite, calcite, mica, quartz, and fluorapatite. Amphiboles and serpentine are associated with certain specific talc deposits. These deposits are rare and historically were used for low-grade industrial applications due to the impurities present.

In 1976, the CTFA issued purity standards for talc.[12] Cosmetic talc consists of a minimum of 90% hydrated magnesium silicate, with remainder consisting of naturally associated minerals such as calcite, chlorite, dolomite, kaolin, and magnesite; it contains no detectable fibrous, asbestos minerals.[30] Additional specifications for cosmetic talc include 6.0% maximum (max) acid-soluble substances; 6.0% max loss on ignition; 3 ppm max arsenic (as As); 20 ppm lead (as Pb); 0.1% max water-soluble substances; no detectable fibrous amphibole (asbestiform tremolite, etc); free crystalline silica (quartz) as specified by the buyer; in a screen test, 100% through 100 mesh, 98% through 200 mesh, and finer grades as specified by the buyer.

As a color additive for drugs, talc sometimes contains a small proportion of aluminum silicate (21CFR73.1550). It is required to meet the specifications for talc listed in the United States Pharmacopeia (USP), and it must also contain not more than 20 ppm lead (as Pb) and not more than 3 ppm arsenic (as As). The following are the acceptance criteria for USP-grade talc: 17.0% to 19.5% magnesium; not more than 0.1% water-soluble substances with neutral pH; no more than 0.25% iron; not more than 10 ppm lead; not more than 0.9% calcium; not more than 2.0% aluminum; and a demonstration of an absence of asbestos.[20] Talc intended for topical application is to have a total aerobic microbial count of not more than 100 cfu/g and a total combined molds and yeasts count of not more than 50 cfu/g; talc intended for oral administration is to have a total aerobic microbial count of not more than 1000 cfu/g and a total combined molds and yeasts count of not more than 100 cfu/g. The acceptance criteria for food-grade talc are not more than 3 mg/kg arsenic and not more than 5 mg/kg lead, and the talc must be derived from deposits that are not associated with asbestos.[36]

Batches of cosmetic talc have been analyzed for asbestos and/or asbestiform minerals throughout the years. Analyses performed in the 1970s that indicated asbestos might be present in talc[37-40] may have used methodology that was unreliable or inaccurate. In the most recent study, which was completed by the FDA in 2012, 9 cosmetic talc suppliers were asked for samples of their talc, 4 complied with the request.[41] The FDA also selected 34 talc-containing retail products. As requested by the FDA, a contract laboratory analyzed the raw material and retail products using polarized light microscopy and TEM, finding no asbestos fibers or structures in any of the samples. The FDA stated that the results were limited, however, because of the limited response by the suppliers and by the number of products tested.

Separate correspondence received by the CIR from the talc industry addressed the issue of the limited response noted earlier from the suppliers of talc.[32] Representatives of the talc industry stated that although not all suppliers of talc (including distributors) contacted by the FDA participated, the study can be considered representative of the US cosmetic talc market as the majority of US cosmetic products were represented.

Sample certificates of analysis were made available from the talc industry.[42,43] One certificate demonstrated that the absence of asbestos was determined using CTFA J 4-1 and USP test methods,[42] and the other stated that the talc products produced by this company do not contain detectable regulated asbestiform minerals.[43]

Production

Talc is obtained from naturally occurring rock ore.[30] Talc commonly forms by hydrothermal alteration of rocks rich in magnesium and iron (ultramafic rocks) and by low-grade thermal metamorphism of siliceous dolomites.[25] Soapstone refers to

impure, massive talc rock;[19] pure talc was once called steatite.[44] Talc is typically mined in open-pit operations,[26] and cosmetic talcs are mined in Italy, France, Norway, India, Spain, China, Egypt, Japan, and the United States.[45]

Crude talc ore can be sorted (beneficiated) to improve the purity of commercial products by either dry or wet processing.[26] In either case, the talc ore is crushed and ground to a fineness suitable for specific end-uses. A dilute talc/slurry water is conditioned for flotation by the addition of a frothing agent (often a low-molecular-weight alcohol), and the slurry is then processed through a series of cells through which air is pumped. This processing causes bubbles to form, and as the bubbles rise to the surface, the talc particles attach to the bubbles due to their organophilic nature; the nontalc impurities are hydrophilic and do not tend to attach to the bubbles. The float (or froth) is then collected. The process is repeated until the desired purity levels are obtained. The talc particles can be further processed by magnetic separation or acid washing to remove iron-bearing minerals, soluble salts, and metals. The talc is then filtered, washed, and dried. Cosmetic talc is typically sterilized by heat treatment.[21]

Use

Cosmetic

Talc is reported to have the following functions in cosmetics: abrasive, absorbent, anticaking agent, bulking agent, opacifying agent, skin protectant, and slip modifier.[1] The FDA collects information from manufacturers on the use of individual ingredients in cosmetics as a function of cosmetic product category in its Voluntary Cosmetic Registration Program (VCRP). The VCRP data obtained from the FDA[46] in 2013 and data received in response to a survey of the maximum reported use concentration by category conducted by the Council[47] in 2009 indicate that talc is used in 3469 cosmetic formulations at concentrations up to 100%; it is used in almost every category of cosmetic product. In 2012, the Council completed a survey to assess the frequency and the use concentration of talc in spray products and the highest reported concentration used in spray products was 35% in a makeup base (aerosol).[48] Frequency and concentration of use data are provided in Table 2.

Products containing talc may be applied to baby skin, used in products that could be incidentally ingested, or used near the eye area or mucous membranes. Additionally, talc is used in cosmetic sprays and powders; for example, talc is reported to be used in face powders at 100%, baby powders at 99%,[47] aerosol makeup bases at up to 35%, and in aerosol deodorants at up to 30%.[48] (Talc is not used in extremely high concentrations in spray or aerosol products because talc clogs the nozzle.[49]) These products could possibly be inhaled. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 µm.[50-53] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (ie, they would

Table 2. Frequency and Concentration of Use—Complete Table in FDA Format and Summary Information by Exposure Type.

	Number of uses[46]	Maximum concentration of use, %[47]
Totals[a]	3469	0.0005-100
Duration of use		
Leave-on	3287	0.002-100
Rinse-off	163	0.0005-70
Diluted for (bath) use	19	0.001-88
Presented in complete FDA VCRP format		
Baby shampoos	NR	7
Baby lotions, oils, powders, and creams	9	99
Bath oils, tablets, and salts	18	1-88
Bubble baths	NR	0.4-2
Bath capsules	1	NR
Other bath preparations	NR	0.001
Eyebrow pencil	47	0.01-79
Eyeliner	122	0.1-90
Eye shadow	1292	20-100
Eye lotion	13	2
Mascara	83	1-50
Other eye makeup preparations	65	2-6
Perfumes	2	2
Fragrance powders (dusting and talcum)	115	15-99
Sachets	3	9
Other fragrance preparations	10	3-9
Hair conditioner	1	0.4
Rinses	NR	0.05
Shampoos	NR	0.04
Tonics, dressings, and other hair grooming aids	2	10
Other hair preparations	2	NR
Hair dyes and colors	NR	0.4-13
Other hair coloring preparations	2	6
Blushers	331	48-94
Face powders	552	20-100
Foundations	211	12-76 (not spray)[48] 1-6 (aerosol spray)
Leg and body paints	3	2 (aerosol spray)[48]
Lipstick	55	3-74
Makeup bases	44	36 (not spray)[48] 35 (aerosol spray)
Rouges	12	NR
Makeup fixatives	11	10
Other makeup preparations	105	0.8-85
Basecoats and undercoats	5	1-7
Cuticle softeners	1	0.004-18
Nail creams and lotions	NR	2
Nail polish and enamel	7	0.002-11
Other manicuring preparations	1	35
Dentifrices	1	NR
Other oral hygiene products	NR	11
Bath soaps and detergents	55	0.001-70
Deodorant (underarm)	18	6-85 (not spray)[48] 1-30 (aerosol spray)
Other personal cleanliness products	30	0.03-20

(continued)

Table 2. (continued)

	Number of uses[46]	Maximum concentration of use, %[47]
Aftershave lotion	1	14
Men's talcum	4	96
Shaving cream	1	NR
Shaving soap (cakes, sticks, etc)	NR	0.04
Other shaving preparations	2	NR
Cleansing	37	0.0005-0.005
Depilatories	4	NR
Face and neck creams, lotions, and powders (excl shaving)	36	40 (not spray)[48] 0.4 (spray)
Body and hand creams, lotions, and powders (excl shaving)	22	96 (not spray)[48] 0.3 (spray)
Foot powders and sprays	10	0.9-97
Moisturizing creams, lotions, and powders	54	3-5
Night creams, lotions, and powders	7	3
Paste masks (mud packs)	28	0.2-18
Skin fresheners	2	0.002-0.2
Other skin care preparations	26	0.03-20
Suntan gels, creams, and liquids	2	15-41
Indoor tanning preparations	4	74
Other suntan preparations	NR	3
Summary information—by exposure type		
Eye area	1622	0.01-100
Incidental ingestion	56	3-74
Incidental inhalation—spray	31[b]	0.3%-35%[48,c]
Incidental inhalation—powder	680	2-100
Dermal contact	3309	0.0005-100
Deodorants (underarm)	18	2-75
Hair—noncoloring	5	0.04-10
Hair—coloring	2	0.4-13
Nail	13	0.002-35
Mucous membrane	160	0.001-88
Baby products	9	7-99

Abbreviations: excl, exclusive; FDA, Food and Drug Administration; NR, not reported; VCRP, Voluntary Cosmetic Registration Program.
[a]The sum of all exposure types may not equal to the sum of total uses.
[b]It is not known whether or not the product is a spray.
[c]In 2012, a survey was completed to assess the use of talc in spray products in which companies were asked whether or not they used talc in spray products, and if so, what is the maximum use concentrate of talc in the spray product and in products that are not sprays in the same FDA product category.

not enter the lungs) to any appreciable amount.[50,52] There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable.[50] However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays.

Studies on exposure during the use of cosmetic talc are summarized in Table 3.[54-56] Many of the researchers noted that there was a wide variation in times and methods for talc use, often by the same volunteer during different applications. Reported application times ranged from 17 to 31 seconds.

The particle size of talc raw material varies widely by product type and by manufacturer but has "no practical significance with regard to human exposure since encapsulation by the other ingredients in the product matrices" (such as a lipstick or deodorant stick) "renders the talc constituents essentially nonrespirable".[26] Semi-solid matrix formulations (typically pressed powders such as blushes, eye shadows, pressed finishing powders, and base powders) incorporate binder systems. Fine talc, with a larger than average particle size (200 mesh), is often preferred for use in blushes, eye shadows, and finishing powders. Loose-talc–based formulations, such as loose finishing makeup powders, baby powders, body powders, and foot powders, do not include a binder system. The majority of cosmetic talcs in loose-matrix powders contain talc particles that are of a larger diameter than those used in other cosmetic applications; for loose powders, a 200 mesh is normally used, and in these loose powders, substantial agglomeration occurs due to electrostatic and crystalline charges on the talc powders.

While some researchers state that the inclusion of a fragrance oil may act as a minimal binder system causing further agglomeration,[26] another researcher found that there was no evidence that the presence of perfume in adult or baby dusting powders containing Italian 00000 grade talc or Chinese talc influenced the level of respirable talc dust.[54]

In the European Union, the use of talc in powdery products intended to be used for children under 3 years is restricted by the requirement of labeling that warns to keep powder away from children's nose and mouth. In Canada, the inner and outer label of preparations in powder form intended for infants and children shall carry cautionary statements to the effect: "Keep out of reach of children," "Keep powder away from child's face to avoid inhalation which can cause breathing problems."[57]

Noncosmetic

Sterile talc is approved as a sclerosing agent.[58] Sterile talc powder is indicated for administering intrapleurally via chest tube to decrease the recurrence of malignant pleural effusions in symptomatic patients. Talc is not allowed for use on the surface of medical gloves.[59]

Talc is used as a color additive in drugs and is exempt from certification and it may be safely used in amounts consistent with good manufacturing practice to color drugs (21CFR73.1550). In foods, talc is used as an anticaking agent, coating agent, lubricating and release agent, surface-finishing agent, and texturizing agent.[36] Talc is generally recognized as a safe substance migrating from cotton and cotton fabrics used in dry food packaging (21CFR182.70) and as a substance migrating to food from paper and paperboard products (21CFR182.90). It is approved as an indirect food additive as a colorant (21CFR 176.170; 21CFR178.3297). According to the World Health Organization, the acceptable daily intake for talc (as magnesium silicate) is "not specified."[60]

The FDA determined that data are inadequate to establish general recognition of the safety of talc as an active ingredient (astringent) in over-the-counter (OTC) drug products (21CFR310.545(e)(18)(ii)).

Table 3. Exposure During Cosmetic Talc Use.

Study population	Test article	Measurement device	Study conditions	Procedure	Respirable amount	Other results	Reference
Infant exposure simulation; number not given	Commercial talcum powder (composition not defined)	Gravimetric dust sampler	Simulated	–Powder was dusted into a shallow tray from a height of 7-13 cm –The air inlets of the sampler were placed where the baby's nose would be, as well as 40 cm above the tray (representing mother's exposure); the dust concentration was similar for the mother and the infant	0.10 mg/min/m^3	10 s dusting period: total median dust concentration—0.243 mppcf 65 s settling period: median dust concentration 0.124 mppcf Median exposure/application: 0.1752 mppcf min Median weekly exposure (5 applications/d): 0.102 mppcf h	55
48 infants	Commercial talcum powder (composition not defined)	10 mm nylon cyclone	Actual	–Mothers diapered infants, applying powder in their usual method –The cyclone inlet was held next to the baby's head, approx 4 in above the change mat –Procedure was repeated 3× in succession and the mean of the 3 runs was used; was performed over two 4-day periods	0.19 ± 0.084 mg/m^3	Avg use/exposure: 0.88 g Exposure time: 0.52 min TWA: 0.095 ± 0.039 mg·min/m^3	56
Adults, 23 males and 21 females	Commercial talcum powder (composition not defined)	10 mm nylon cyclone	Actual	–Patients applied powder in their usual manner in an anteroom –A headband with an attached 10-mm cyclone positioned at the level of the nose was worn –Performed over two 4-day periods	2.03 ± 1.49 mg/m^3	Avg use/exposure: 8.84 g Exposure time: 1.23 min TWA: 1.727 mg·min/m^3	
Infant simulation; 4 participants	Baby powder with: –Chinese talc –Italian 00000 grade talc (cosmetic talcs; both perfumed and unperfumed; Chinese and Italian perfumed talc contained 0.045% and 0.2% perfume, respectively)	For respirable dust: cyclone elutriator/filter head system with 25-mm diameter filter; allowed sampling of all particles <1 μm, 50% of 5-μm particles, and no 7-μm particles For total dust: cyclone removed and open filter holder with a 37-mm filter	Simulated	–In a 3.7 × 2.8 m^2 room, adult participants used a doll to simulate powdering during diapering –The sample collection unit was on a table next to the doll's head –The "doll's nose" was approx 15-30 cm from the sampling point –Sampling time was 5 min –2 trials at 1-hour intervals	Chinese, perfumed: <0.1-0.9 mg/m^3; unperfumed: <0.1-0.9 mg/m^3 Italian, perfumed: <0.1-0.3 mg/m^3; unperfumed: <0.1-0.5 mg/m^3	–There were no major differences among concentrations of respirable dust –Mean concentration of respirable talc (for Chinese and Italian perfumed and unperfumed talcs)—0.21 mg/m^3 – Respirable talc accumulated during 4 samplings: 0.005-0.3 mg/m^3 – No evidence that perfume affected amount of respirable talc – Mean talcing time: 19-21 s	54
4 Female participants	Loose face powder: –Chinese talc –Italian 00000 grade talc –Italian micronized-grade talc (cosmetic talcs; all unperfumed)	As above	Actual	–In a 2 × 1 m^2 room, participants applied powder in their normal manner (a small window was open during application) –The application puff was only dipped once in the powder –The participant's nose was approx 15 cm from the sampling point –Sampling time was 5 min –Two trials at 1-hour intervals	Chinese: <0.1-1.1 mg/m^3 Italian: <0.1-0.8 mg/m^3 Italian, micronized: <0.3-1.7 mg/m^3	With the exception of micronized talc, there were no major differences among concentrations of respirable dust –Mean concentration of respirable talc (for Chinese and Italian perfumed and unperfumed talcs)—0.48 mg/m^3 –Respirable talc accumulated during 4 samplings: 0.1-0.4 mg/m^3 –No evidence that perfume affected the amount of respirable talc –Mean talcing time: 17-19 s	

(continued)

Table 3. (continued)

Study population	Test article	Measurement device	Study conditions	Procedure	Respirable amount	Other results	Reference
4 female participants	Adult dusting powder: –Chinese talc –Italian 00000 grade talc (both perfumed and unperfumed) –Italian micronized-grade talc, unperfumed (cosmetic talc)	As above	Actual	–In a 2.3 × 2 m^2 room, participants applied powder in their normal manner –The participant's nose was approx 30-90 cm from the sampling point –One experiment with unperfumed Italian talc was performed at >90% humidity –Sampling time was 5 min –Particle size analysis was performed for unperfumed Italian 00000 and micronized talc Two trials at 1-hour intervals	Chinese, perfumed: 0.3-2.6 mg/m^3; unperfumed: 0.5-1.8 mg/m^3 Italian, perfumed: 0.4-1.7 mg/m^3; unperfumed: 0.5-2.6 mg/m^3 High humidity: 0.2-0.8 mg/m^3 Italian, micronized: 0.6-3.3 mg/m^3	–With the exception of micronized talc, there were no major differences among concentrations of respirable dust –Mean concentration of respirable talc (for Chinese and Italian perfumed and unperfumed talcs)—1.13 mg/m^3 –Mean concentrations of micronized talc were 1.9 mg/m^3 –Respirable talc accumulated during 4 samplings: 0.3-2.5 mg/m^3 Total talc with cyclone removed: Italian 00000 unperfumed, 2.7-4.8 mg/m^3; Italian micronized, 0.2-1.5 mg/m^3 –Total talc with cyclone removed: Italian 00000 unperfumed, 2.7-4.8 mg/m^3; Italian micronized, 0.2-1.5 mg/m^3 –Total talc with open filter: Italian 00000 unperfumed, 8-27 mg/m^3; Italian micronized, 10-17 mg/m^3 –Detectable background levels of respirable talc were found only with micronized talc (0.6-1.6 mg/m^3) and Italian talc (<0.1-1.0 mg/m^3) at high humidity –No evidence that perfume affected the amount of respirable talc –Particle size analysis demonstrated that most particles were between 1 and 8 μm Mean talcing time: 27-31 s	
Adult consumers and miners	Consumer—cosmetic talc; miner—talc dust	Not stated	Actual	Comparison between adult consumer's 1 min daily exposure and a miner's 8 hour daily exposure		–Consumers: weekly exposure resulting from use lasting 10 s, with 65 s settling time, would be 0.102 mppcf-h of talc dust/wk –Miners: assuming a max daily exposure of 20 mppcf talc dust, weekly exposure would be 890 mppcf h –Exposure of miners about 8000× greater than that of consumers (calculations were not provided)	55

Abbreviations: Avg, average; max, maximum.

Talc is used as a dusting powder, alone or with starch or boric acid, for medicinal and toilet preparations.[61] It is used as an excipient and filler for pills and tablets, for dusting tablet molds, and for clarifying liquids by filtration. Talc is also used as a pigment in paints, varnishes, and rubber; as a filler for paper, rubber, and soap; in fireproof and cold-water paints for wood, metal, and stone; for lubricating molds and machinery; as glove and shoe powder; and as an electric and heat insulator. Talc is used in the leather industry, in the roofing and ceramic tile industry, as a carrier for insecticides and herbicides,[55] and it is used in plastics.[27]

Toxicokinetics

Inhalation

Nonhuman. To determine the deposition, distribution, and clearance of talc, 44 female Syrian golden hamsters received a single 2-hour nose-only exposure to a neutron-activated talc aerosol and subgroups of 4 animals were then killed at 11 different intervals from 15 minutes to 132 days after exposure.[62] The talc tested was a commercial baby powder. (Chemical characterization data were not provided). Nine unexposed control animals were used, of which 4 were killed on the day the test animals were exposed and 5 were killed on the final day of the study. The aerosol exposure system had 7 tiers of exposure ports, and the talc aerosol was passed through a cyclone elutriator to remove particles that were larger than ~10 μm in diameter; the activity median aerodynamic diameter was 6.4 to 6.9 μm. The mean aerosol concentration was 40 and 75 μg/: at the 15 to 30 and 60 to 90 min sampling periods, respectively. In the presentation of the results, the γ-ray counts from the controls were expressed as μg talc equivalent, and the γ-ray counts of the exposed animals were not corrected for control values.

Variations among animals killed at the same time were attributed to variations in aerosol concentration at different tiers. The mean pulmonary talc content in the lungs of test animals at various time intervals was 33.08 (15 minutes after exposure), 24.08 (100 minutes), 42.70 (4 hours), 18.75 (21 hours), 21.30 (2 days), 21.03 (after 4 days), 13.85 (after 8 days), and 8.95 μg (after 18 days); the mean for the day 0 control animals was 1.78 μg. The biological half-life of the talc deposited in the lungs was 7 to 10 days. At the time of termination of the final group, that is, 132 days, there was no statistically significant difference in the talc burden of the lungs of test (3.70 μg) and control (2.30 μg) animals. The amount of talc in the liver, kidneys, and lungs was also determined; the only statistically significant differences compared to controls in any of these organs were found in the liver; there was a decrease at 4 hours compared to day 0 controls, an increase at day 36 compared to both days 0 and 132 controls, and an increase on day 68 compared to day 132 controls. Analysis of the data using the Kruskal-Wallis test showed that there were no significant differences among the mean talc burden values for the liver, kidneys, and ovaries, including the control values, and that there was no significant trend, indicating there was no translocation of talc to these tissues. As noted, no translocation from the respiratory tract to other tissues was found in this study, and the clearance of talc from the lungs was complete within 4 months after exposure.

Oral

Nonhuman. Six female Syrian golden hamsters (outbred Ela: ENG strain) were dosed by gavage with 1 mL neutron-activated talc suspended in physiological saline containing 0.6% (w/w) 1% methyl cellulose (concentration not specified), and the animals were killed 24 hours after dosing.[63] The talc used was a commercial baby powder. (Chemical characterization data and particle size were not provided). Four hamsters were dosed similarly with a nonirradiated talc solution. The neutron-activated talc was exposed to an integrated neutron flux of 7×10^{16} n/cm^2 30 days prior to dosing. The skinned carcass, gastrointestinal (GI) tract, lungs, liver, kidneys, and excreta were analyzed for ^{60}Co and ^{46}Sc by γ-ray spectrometry, and the γ-ray counts were compared with those of 4 hamsters that were not dosed with talc.

The γ-ray counts of the tissue and excreta of the dosed animals were equivalent to a total of 2.94 mg talc. Based on γ-ray counts, 74.5% of the neutron-activated talc was recovered in the feces and 23.5% was recovered in the GI tract, while 1.91% was recovered in the skinned carcass, 0.09% in the urine, 0.04% in the kidneys, and 0.02% in the liver. The amount found in the urine of the hamsters given irradiated talc was statistically significantly increased compared to the controls. No talc was recovered in the lungs.

The absorption, distribution, and excretion of orally administered talc were determined in mice, rats, and guinea pigs.[64] (Chemical characterization data were not provided). With all species, [^{3}H]talc was administered as a suspension in aqueous (aq) glycerol jelly solution (10 mg/mL; 1 μCi/mL). Four LACA female mice were given a single oral dose of 40 mg/kg body weight (bw) [^{3}H]talc. Two mice were killed at 6 hours and 2 at 24 hours after dosing. In the mice killed 6 hours after dosing, 95% and 96% of the radioactivity was recovered in the large intestines and feces, 9% and 7% was recovered in the small intestines and stomach, and 0.7% and 0% in the urine of each mouse. In the 2 mice killed at 24 hours after dosing, 99% and 101% of the radioactivity wasrecovered in the large intestines and feces, 4% and 6% was recovered in the small intestines and stomach, and 1.3% and 1.5% in the urine of each mouse. Less than 0.005% of the radioactivity was found in the carcass of any of the mice.

Three male Wistar albino rats were given a single oral dose and 3 rats were given 6 daily oral doses by gavage of 50 mg/kg bw [^{3}H]talc. After the last dose, urine and feces were collected every 24 hours for 4 days and on day 10 and then the rats were killed. Within 24 hours after administration of the single dose, approximately 75% of the radioactivity was recovered in the feces and only 1% was recovered in the urine. After 96 hours, a total of 95.8% of the dose was excreted in the feces and 1.7% in the urine, with a total excretion of 97.5% of the dose. No radioactivity was recovered in the liver or kidneys 10 days after a single dose of talc.

On day 10 in the rats given 6 daily doses of [^{3}H]talc, there was no radioactivity found in the feces or livers, and there was a trace of radioactivity (<0.02%) in the kidneys of these rats.

Three female Dunkin Hartley guinea pigs were administered a single oral dose of 25 mg/kg bw [^{3}H]talc, and urine and feces were collected as described previously; all animals were killed on day 10. Talc was excreted more slowly in the guinea pig than in the rat. Within 24 hours after dosing, 31% of the radioactivity was recovered in the feces, and 0.2% was recovered in the urine. At 24 to 48 and 48 to 72 hours after dosing, 39% and 19% of the radioactivity, respectively, was recovered in the feces, with <0.01% of the dose being recovered in the urine at each of these time periods. Within 96 hours of dosing, a total of 94.4% of the radioactivity was recovered in the feces and 0.2% was recovered in the urine, with a total of 94.6% of the dose being excreted over 96 hours.

Intrapleural

Nonhuman. Wistar rats were used to determine the systemic distribution of talc following intrapleural administration.[65] Groups of 20 rats (sex not specified) were administered 10 or 20 mg talc in 1 mL of saline as a slurry into the pleural cavity. (Chemical characterization data were not provided). Ten animals of each group were killed 24 hours after instillation, and the remaining 10 animals were killed 48 hours after instillation. The lungs, chest wall, liver, kidneys, spleen, heart, and brain of each animal were removed for examination. There were no gross lesions in the examined tissues. Microscopic examination revealed that the chest wall had the most common lesions, and these lesions were represented by an early pneumoconiosis characterized by stellate interstitial collections of dust-laden macrophages containing pale yellow particles associated with inflammatory infiltrate of lymphocytes with mild fibroblastic proliferation. Polarized light used to locate birefringent particles revealed "large numbers of irregular, strongly birefringence platy, acicular, and 'Maltese Cross' crystals that varied in length from 5.7 to 70 μm" in the chest wall. The deposition index of talc crystals was greater in the chest wall and the lungs after administration of 10 mg (3.90 in the chest and 3.18 in the lungs) than 20 mg talc (3.58 in the chest and 2.50 in the lungs); this difference was statistically significant. (It is not stated whether these values were from the 24-hour group, 48-hour group, or an average of the 2). Pneumoconiosis reactions were not observed in the other organs; however, talc crystals were present inside the microvessels of these organs. The researchers suggested talc was absorbed rapidly through the pleura, reaching the systemic circulation with deposition in other organs within 24 hours after administration, and that the distribution was not dose related.

Toxicological Studies

Single Dose Toxicity

Oral. The median lethal dose (LD_{50}) of talc in rats was determined to be 920 mg/kg bw.[66] Ten male rats were dosed by gavage with 5000 mg/kg bw talc suspended in 0.85% saline; all 10 rats died within 24 hours. Groups of 5 rats were then intubated with 50, 100, 500, 1000, 2000, or 3000 mg/kg bw talc in saline. All 5 animals dosed with 3000 mg/kg bw, 4 dosed with 2000 mg/kg bw, 3 with 1000 mg/kg bw, and 1 with 500 mg/kg bw talc died. (Chemical characterization data were not provided).

In another single-dose study in rats, the LD_{50} was >5000 mg/kg bw.[66] All the animals survived dosing with 5000 mg/kg bw talc in 0.85% saline.

The oral LD_{50} of 18.3% talc in saline was >5000 mg/kg bw.[66] A single oral dose of 5000 mg/kg bw of talc prepared as an 18.3% (w/v) suspension in saline was administered to 10 male rats. All animals survived, and there were no signs of toxicity.

Inhalation. Eight mice were placed in a box with baby powder that was circulated with compressed air.[67] (Details regarding the composition of the baby powder, the amount of baby powder, or the size of the box were not provided). Two mice were removed from the box at 30-minute intervals, that is, after 30, 60, 90, or 120 minutes. The mice removed after 30 and 60 minutes recovered completely; symptoms that were observed were not specified. The mice removed after 90 minutes died in 5 to 6 hours; the mice removed at 120 minutes died immediately upon removal. The mice that died were necropsied, and the mucous membrane of the airway was found covered with baby powder. Microscopically, hemorrhage, edema, and desquamation of bronchial epithelium admixed with baby powder were observed.

Intrabursal. Groups of 10 anesthetized female Sprague-Dawley rats (10-15 weeks of age) were given a single bilateral intrabursal injection of 100 μL of 100 mg/mL talc in phosphate-buffered saline (PBS) into the bursa around the ovaries, and groups of 3 age-matched, sham-operated, and sham-treated rats were used as controls.[68] Asbestos-free Italian 00000 talc, composed of platy crystals ranging in size from 0.3 to 14 μm, was used. The animals were killed 1, 3, 6, 12, or 18 months after dosing. There was no effect on the production of physiological concentrations of steroid hormones. Gross examination was made for all animals, and microscopic examination was performed 12 months after dosing. One or both ovaries of rats dosed with talc were cystic in appearance at all time periods; no gross changes were seen in the ovaries of the control animals; the cystic structures were not derived from the ovaries but were due to distention of the bursal sac. Focal areas of papillary change were seen in the surface epithelium of 4 injected ovaries but not in any of the controls. There was no correlation between the presence of foreign body granulomas and the presence of the papillary changes. No evidence of cellular lesions or of mitotic activity was seen in the nonpapillary areas of the surface epithelium of injected ovaries, and neoplasia was not observed. Foreign body granulomas, without surrounding inflammation, were seen in the cortical area of 5 of the injected ovaries, with similar lesions in the supracapsular

fat in the connective tissue matrix of the capsule. Talc was observed in the granulomas.

Intraperitoneal. The induction of fibrosis following an ip injection of 50 mg/kg bw nonfibrous talc in physiological saline was evaluated in 6 male and 6 female Wistar rats.[69] A granulomatous reaction in which foreign-body giant cells containing refractile materials was observed in the rats at 1 month after dosing, and this lesion was still observed at 3 months but there was no fibrosis.

Groups of 5 female Wistar rats were used to evaluate the toxicity of talc following a single ip injection of 0.02, 0.1, or 0.5 g in 5 mL normal saline.[70] Although the talc was described as irregular crystalline plates, it was also stated that it could vary from all plates to all fibers. The talc was composed of 49% to 56% silicon dioxide, 20% to 22% magnesium oxide, and 6% to 8% calcium oxide; the particle size ranged from 10 to 120 μm, with a mode of 20 μm. The control group was administered saline only. The animals were killed 7 days after dosing. There were no adhesions in the control group, but adhesions were observed, mainly in the upper abdomen, in the test animals; 3 animals of the 0.5 g group had mild/intermediate adhesions and 4 animals in the 0.5 g group had 4 intermediate adhesions. Talc particles could be seen in the adhesions. The parietal peritoneal mesothelium was examined microscopically using the Hautchen technique, and clusters of foci of inflammatory cells were observed scattered on the surface of the peritoneum. Again, talc particles were seen in the center of each focus of inflammatory cells. Powder deposits adherent to the viscera or omentum without adhesions were reported in 3 animals dosed with 0.02 g talc and in all animals dosed with 0.1 or 0.5 g talc; ascites did not occur in any of these animals.

Cellular effects. Cellular effects in various systems are described in Table 4. There were no remarkable results found in studies examining the cellular effect of talc, such as cytotoxicity assays, assays examining the effect of talc on cell viability, or studies on the induction of apoptosis (among others).[69,71-78]

Repeated Dose Toxicity

Repeated dose animal toxicity studies are summarized in Table 5. Dermal application of talc to shaved rabbit skin for 6 weeks resulted in dryness of the skin and skin erosion.[79] Oral administration to rats for 5 days produced minimal toxicity[66]; no toxicologically significant effects were noted in a 5-month study in which rats were fed a diet containing 100 mg/d Italian talc.[80] In inhalation studies, exposure of mice and rats for 4 weeks (25 μm particle size) resulted in macrophages in the alveolar space, with more found in the mice than in the rats.[10,81] In rats exposed for 3, 6, or 12 months, minimal to slight fibrosis resulted.[80] In hamsters, exposure by inhalation to baby powder (95% talc; 4.9-6.0 μmol/L) for 30 days did not result in clinical toxicity.[82] Intrapleural administration of talc (25 μm) to rats did not result in mesotheliomas; granulomas at the injection site were common.[80] Infections occurred, but no neoplastic or perineal changes, when talc was instilled intravaginally or perineally in rats.[83] Upon intravenous (iv) injection of talc (<5 μm) once weekly for 3 weeks in guinea pigs, talc was found in the lungs and the liver throughout the study.[84]

Ocular Irritation

Two unpublished ocular irritation studies were briefly summarized in the International Uniform Chemical Information Database data set on talc.[85] Talc was not irritating to the eyes of rabbits in 1 study and was slightly irritating to the eyes of rabbits in the other study. No details were provided.

A case study was reported in which a woman presented with a foreign body sensation and inflammation of the conjunctiva of both eyes.[86] Following a biopsy and electron microscopy and electron diffraction analysis of the sample, a diagnosis of foreign body granuloma secondary to talc was made. It was postulated that the talc originated from surgical gloves used during a surgery performed decades earlier.

Granuloma Formation in the Skin

Application of talc on wounds can give rise to scab formation, possible infection, and foreign body granulomas in the dermis.[87] In 1 case study, talc powder applied to postvaricella lesions resulted in granulomas. In another case study, hundreds of granulomas of the skin developed in a patient that had open, draining furuncles and who had liberally applied talc daily.[88]

Occupational Exposure

Talc has a threshold limit value (TLV; respirable fraction) of 2 mg/m^3 as a 10-hour time-weighted average (TWA).[89] The National Institute for Occupational Safety and Health states the immediately dangerous-to-life-or-health concentration is 1000 mg/m^3. The Occupational Health and Safety Administration mineral dust limit for talc is 20 million of particles per cubic foot (mppcf) of air, if containing less than 1% quartz; if ≥1% quartz is present, then the quartz limit is used (250/[%SiO_2 + 5] mppcf) (29CFR1910.1000 Table Z-3).

Human pulmonary effects of chronic occupational inhalation of talc include diffuse interstitial fibrosis and progressive massive fibrosis (often called complicated pneumoconiosis).[90] Depending on the composition and contaminants of talc, 3 forms of talc-related pulmonary effects have been described: pure talcosis, produced by exposure to talc that is free of silica and asbestiform minerals; talco-asbestosis, produced by the inhalation of talc with asbestiform fibers; and talcosilicosis, produced by exposure to talc associated with silica and other nonasbestiform fibers.[91] A fourth talc-related disease, stemming from iv administration of talc, is not related to occupational exposure but instead is usually associated with abuse of oral medications. Each form has a distinctly different radiographic appearance. The radiographic abnormalities associated with pure talcosis consist of small nodules that are usually seen in the lower pulmonary fields. Reticulations may occur but this

Table 4. Cellular Effects.

Talc/composition	Particle size	Test system	Procedure	Results	Reference
Talc, nonfibrous	Not specified	Peritoneal and alveolar macrophages	Cytotoxicity assay	Low cytotoxicity –Cytotoxicity of talc and other dusts was compared to induction of fibrosis following ip injection in Wistar rats; there was a good correlation between cytotoxicity of dust to macrophages in vitro and fibrogenicity in vivo	69
Talc; cosmetic grade (5 samples) 1 sample with 30%-35% chlorite 1 sample with 1%-3% amphiboles	4 cosmetic-grade samples: 80%-91.5% of the respirable dust (1.94%-7.36% of the sample) was <7.5 μm; micronized cosmetic talc: 93.5% of the respirable dust (19.46% of the sample) was <7.5 μm; chlorite and amphiboles samples: 3.62% and 9.76% respirable dust, respectively	Unstimulated mouse peritoneal macrophages	Cytotoxicity of the 7 talc samples was determined and compared to that of a standard quartz sample and a nonfibrogenic dust (magnetite)	–All 7 talc samples were cytotoxic to macrophages, but far less so that the quartz sample; quartz content of each talc (which ranges from <0.2% to 0.7%) did not seem to affect cytotoxicity –The activity of each of talc sample was similar to that of the others and not related to particle-size distribution –The talc samples induced a statistically significantly greater release of LDH compared to magnetite, and they caused a slightly but significantly greater release of lysosomal β-glucuronidase than of LDH from the macrophages	73
Talc, Italian 00000	≤10 μm	Rabbit lung fibroblasts	Ingestion of talc particles by fibroblasts was determined	–Talc was taken up by fibroblasts, and the talc particles were observed in the cells	74
Talc, Italian	Not provided	V79-4 Chinese hamster lung cells; human alveolar type II lung cells (A549)	Cytotoxicity was determined	–50 μg/mL was not cytotoxic to V79-4 cells –Talc inhibited the growth of A549 cells, the inhibitory concentrations and extent of the inhibition were not reported	72
Talc; composition not provided but assumed to be cosmetic grade	Not provided	OSE2a; GC1a	Effect of talc on cell viability; cell cultures were incubated with 0-500 μg/mL talc for 24-120 hours	–OSE2a cells: cell viability was statistically significantly increased with 5 μg/mL talc at 24 hours and statistically significantly decreased at 200 μg/mL after 72 hours and at 500 μg/mL after 24 and 72 hours –GC1a cells: viability was statistically significantly increased at 5, 20, and 100 μg/mL talc after 72 hours and was statistically significantly decreased at 500 μg/mL after 24 hours	71
As above		OSE2a; GC1a	Neoplastic transformation assay	–OSE2a cells: compared to untreated controls, a statistically significant increase in the number of transformed colonies was seen at 5 and 20 μg/mL, but a statistically significant decrease in transformed cells was seen at 100 μg/mL –GC1a cells: 5, 20, and 100 μg/mL talc caused a statistically significant increase in transformed colonies	
As above		OSE2a; GC1a; human PMN	Ability to induce ROS	–OSE2a and GC1a cells: initial concentration-dependent decrease in ROS generation (at 24 hours); ROS generation then increased in both cell lines, and the increase was statistically significant at 20 μg/mL at 72 and 120 hours and at 50 μg/mL at 120 hours in the OSE2a cells and at 0.5, 20, and 20 μg/mL at 72 and 120 hours and at 5 and 100 μg/mL at 120 hours compared to the 24-hour value –PMN: a concentration-dependent increase in the induction of ROS, and the increase was statistically significant at 0.5, 5, 20, and 50 μg/mL at 24 hours and at 100 and 500 μg/mL at 24 and 72 hours; the maximum ROS generation in PMN was seen at 500 μg/mL talc at 24 hours, and the increase was 4-fold compared to untreated controls	

(continued)

Table 4. (continued)

Talc/composition	Particle size	Test system	Procedure	Results	Reference
Talc, composition not provided	2 μm	PMC; LAC (A549)	Cells were exposed to 25, 50, and 75 μg/mL talc suspended in endotoxin-free normal saline for 24, 48, and 72 hours to determine the ability to induce apoptosis	–Talc induced apoptosis of LAC in a concentration- and time-dependent manner, but talc did not induce apoptosis of PMCs	75
Talc in endotoxin-free water (assumed to be pharmaceutical grade)	2.1 μm	PMC	Confluent PMCs were exposed to 2-64 μg/cm^2 sterilized talc for 24 hours	–PMC viability decreased with increasing talc concentrations; viability with 64 μg/cm^2 was 75% –All concentrations of talc significantly stimulated the release of IL-8 and MCP-1 over that of unstimulated cells –Talc significantly increased chemotactic activity for neutrophils and monocytes compared to unstimulated cells; the addition of excess IL-8 or MCP-1 antibody decreased chemotaxis, but it did not return entirely to the level of unstimulated cells – Talc induced C-X-C and C-C chemokine expression; the transcriptional response of IL-8 and MCP-1 expression was enhanced – Talc induced intercellular adhesion molecule 1 (ICAM-1) expression on PMC	76
As above			Confluent PMCs were exposed to 4 μg/cm^2 sterilized talc for 1-72 hours; controls were exposed to 4 μg/cm^2 glass microspheres	–Talc stimulated production of IL-8 and MCP-1 to a greater degree than did glass beads	
Talc in endotoxin-free 0.89% normal saline (4.0 mg/mL; assumed to be pharmaceutical grade)	2.1 μm	PMC; MMC	Confluent cells were exposed to 0-24 μg/cm^2 sterilized talc in serum-free medium for 72 hours; controls were exposed to 4 μg/cm^2 glass microspheres; viability was determined	–PMC viability was 93% with 24 μg/cm^2 talc –MMC viability decreased with increasing concentration of talc; with 24 μg/cm^2 talc, viability ranged from 62%-84% depending on the cell line	77
As above			Confluent cells were exposed to 0-24 μg/cm^2 talc in serum-free media for 24 hours; apoptosis was determined by TUNEL	–PMC did not show significant apoptosis with varying concentrations –Talc induced apoptosis in MMC in a concentration-dependent manner; significance was noted at 6 μg/cm^2 and then plateaued	
As above			PMC/MMC confluent cells were exposed to 4 μg/cm^2 talc for 24-72 hours; 6 μg/cm^2 glass microspheres were used as controls; TUNEL and DNA electrophoresis was performed	–Apoptosis of PMC cells by talc did not increase with time –Talc induced apoptosis in MMC in a time-dependent manner; the increase over time was statistically significant compared to controls –A typical DNA ladder indicative of apoptosis was seen with MMC but not with PMC	
Talc, nonfibrous; mean surface area—16.03 m^2/g	1.1 μm	LP9; IOSE	Effect on cell viability was determined LP9 cells: changes in gene expression were measured with 15 and 75 μm/cm^2 at 8 hours and 15 μm/cm^2 at 24 hours IOSE cells: changes in gene expression were measured with 75 μm/cm^2 at 8 and 24 hours	Nontoxic to IOSE cells at up to 75 μm^2/cm^2 and to LP9 cells at ≤163 μm^2/cm^2; toxicity seen with ≥243 μm^2/cm^2 –LP9 cells: low conc of talc increased expression of 1 gene at 8 hours and no changes at 24 hours, while elevated expression levels of 30 genes were seen at 8 hours with high conc –IOSE: no significant mRNA changes	78

Abbreviations: GC1a, normal ovarian granulosa cells; IL-8, interleukin 8; IOSE, human ovarian epithelial cells; LAC, lung adenocarcinoma cell line; LDH, lactate dehydrogenase; LP9, human mesothelial LP9/TERT-1 cells; MCP-1, monocyte chemotactic protein 1; MMC, human malignant mesothelioma cells; OSE2a, normal ovarian epithelial cells; PMC, human pleural mesothelial cells; PMN, polymorphonuclear neutrophils; ROS, reactive oxidative species; TUNEL, terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick end labeling; conc, concentration; mRNA, messenger RNA; ip, intraperitoneal.

Table 5. Repeated Dose Toxicity Studies.

Talc/composition	Particle size	Dose/conc	Animals; #/grp	Dose duration	Procedure	Results	Reference
Dermal							
Commercial talcum powder; composition not provided	Not provided	Amount applied was not specified	Domestic rabbits 5 M/5 F (test grp) 4 M/4 F (controls)	1×/d 6 wk	–The powder was sprinkled on the shaved skin of the dorsal surface of the body trunk and then spread evenly over the site –It does not state that the site was wrapped – Blood chemistry values were measured at the termination of dosing	–All animals developed skin dryness –Signs of skin erosion were observed – No clinical signs were observed – Compared to control values: – Alanine transaminase, aspartate transaminase, glutamyl transferase, amylase, and potassium ion values were statistically significantly decreased – Cholesterol, high-density lipoproteins, triglycerides, bilirubin, and glucose values were statistically significantly increased	79
Oral							
Talc; composition not provided	Not provided	29.6% in saline 5000 mg/kg bw/d	5 rats	5 days	No additional details	Minimal signs of toxicity were observed	66
Italian talc, 00000 grade; 92% talc (by wt), 3% chlorite, 1% carbonate minerals; 0.5%-1% quartz	25 μm (mean particle size); upper size, 70 μm	100 mg/d in feed	Wistar rats 16 M/16 F (talc and chrysotile) 8 M/8 F (controls)	101 days over 5 mo	Super-fine chrysotile asbestos (SFA chrysotile)-fed and untreated controls were used; 2 animals/group were killed 3 mo after dosing, all other animals lived until natural death	–Talc: mean survival (from start of feeding), 614 days; 1 leiomyosarcoma of the stomach, 2 sarcomas of the uterus –Chrysotile: mean survival, 619 days; 1 possible leiomyosarcoma of the stomach, 1 sarcoma of the uterus, 1 lymphosarcoma – Controls: mean survival, 641 days; 1 adrenal adenoma	80
Inhalation							
Asbestos-free talc; 19.2%-19.4% Mg	MMAD, 2.7 ± 0.1 μm; 79% of the talc by mass had an aerodynamic diameter <5 μm	Target: 0, 2, 6, or 18 mg/m^3 Actual: 0, 2.2, 5.7, or 20.4 mg/m^3	B6C3F$_1$ mice 10 M/10 F	4 wk 6 h/d 5 days/wk	–Multitiered inhalation chambers were used; animals were killed 24 hours after the last exposure; lung burdens were measured in half of the animals and the other half were used for microscopic examination –This study was used to determine the exposure concentrations for a 2-yr NTP bioassay	–Lung burden averaged 0, 100, 290, and 1020 μg talc/g lung for control, low, mid, and high doses, respectively; lung burdens normalized for lung wt and exposure conc: n/a, 46, 51, and 50 μg talc/g lung/mg/m^3, respectively No exposure-related abnormalities were seen at necropsy; microscopically, the only exposure-related lesion was a modest, diffuse increase in free macrophages within the alveolar space; the macrophages, which were focally aggregated, contained talc particles	10,81
Asbestos-free talc; 19.2%-19.4% Mg	MMAD, 3.3 ± 0.1 μm; 79% of the talc by mass had an aerodynamic diameter <5 μm	Target: 0, 2, 6, or 18 mg/m^3 Actual: 0, 2.3, 4.3, or 17 mg/m^3	F344/Crl rats 10 M/10 F	4 wk 6 h/d 5 days/wk	–As above –This study was used to determine the exposure concentrations for a lifetime NTP study	–Lung burden averaged 3, 70, 170, and 720 μg talc/g lung for control, low, mid, and high doses, respectively; lung burdens normalized for lung wt and exposure conc: n/a, 30, 39, and 42 μg talc/g lung/mg/m^3, respectively; normalized low-dose value was statistically significantly greater than mid- and high-dose values –The increase in talc lung burden with exposure concentrations may be attributable to overwhelming the capacity of the respiratory tract to clear particles at 6 and 18 mg/m^3 exposures – No exposure-related abnormalities were seen at necropsy; microscopically, the only exposure-related lesion was a modest, diffuse increase in free macrophages within the alveolar space; fewer macrophages were seen in the exposed rats than in the exposed mice; the diffusely scattered macrophages contained talc particles	10,81

(continued)

Table 5. (continued)

Talc/composition	Particle size	Dose/conc	Animals; #/grp	Dose duration	Procedure	Results	Reference
Italian talc, 00000 grade; 92% talc (by wt), 3% chlorite, 1% carbonate minerals; 0.5%-1% quartz	25 μm (mean particle size); upper size, 70 μm	10.8 mg/m^3 (mean) approximately 40% respirable	Wistar rats	7.5 h/d 5 days/wk	Animals (6/cage) were exposed to talc dust; SFA chrysotile controls were treated similarly at each time frame; untreated controls were used; some animals were killed 10 days or 1 yr after final exposure, and the remainder lived until natural death	Mean fibrosis scoring scale: 1—nil; 2—minimal; 4—slight; 6—moderate; 8—severe (for use below)	80
		Cumulative 3 mo dose = 4100 mg/m^3 h	24 M/24 F	3 mo	8 Animals were killed 10 days and 8 were killed 1 yr after exposure	–Mean fibrosis score 10 days/1 yr after talc exposure: 2.2/2.4; chrysotile: 2.8/2.2; controls: 1.8/1.6 –Over 50% of the animals were alive at 28 mo	
		Cumulative 6 mo dose = 8200 mg/m^3 h	12 M/12 F	6 mo	6 Animals were killed 10 days after and 4 talc and chrysotile animals and 3 control animals were killed 1 yr after exposure	–Mean fibrosis score 10 days/1 yr after exposure –Talc: 2.7/3.4; chrysotile: 3.0/3.2; controls: 1.9/1.5 – Most test animals died by 28 mo; there were no lung tumors in the talc or control group and 1 adenomatosis in the chrysotile group	
		Cumulative 12 mo dose = 16 400 mg/m^3 h	12 M/12 F	12 mo	6 Animals were killed 10 days after exposure and 4 talc and chrysotile animals and 3 control animals were killed 1 yr after exposure	–Mean fibrosis score 10 days/1 yr after exposure –Talc: 3.4/4.6; chrysotile: 3.2/4.2; controls: 1.3/1.9 – Most test animals died by 28 mo; in the lungs, 1 adenoma was found in the talc group; 3 adenomas, 2 adenomatosis, and 1 adenocarcinoma was found in the chrysotile group; there were no lung tumors in the controls	
Commercial (talc) baby powder; 95% (w/w) platy talc with trace quantities of carbonates (magnesium and dolomite) and platy chlorite and rutile	MMAD, 4.9 μm	37.1 ± 7.4 μg/L (MTAC) Respirable fraction: 9.8 ± 2.4 μg/L Cumulative dose: 3 min: 14.6 $mg{\cdot}h/m^3$ 30 min: 146 $mg{\cdot}h/m^3$ 150 min: 732 $mg{\cdot}h/m^3$	Syrian golden hamsters, 50 M/50 F; controls. 25 M/25 F	30 days 3, 30, or 150 min/d 5 days/wk	Single-tier exposure; animals lived until natural death	–No statistically significant difference in survival time among groups, but there was a significant difference between males and females within grps; no clinical signs of toxicity to talc –The type, incidence, and severity of lesions indicated no trend toward a dose–response and no statistically significant differences between exposed and control groups	82
Talc; "technical" or "pharmaceutical" grade	Not provided	30-383 mg/m^3	Rats; number not provided	9 mo; 6 h/d, 6days/wk	Details were not provided	None of the animals died as a specific consequence of exposure	85
Intrapleural							
Italian talc, 00000 grade; 92% talc (by wt), 3% chlorite, 1% carbonate minerals; 0.5%-1% quartz	25 μm (mean particle size); upper size, 70 μm	20 mg in physiological saline; 50 mg/mL	Wistar rats 24 M/24 F	Until natural death	Injection into the right pleural cavity; saline and SFA chrysotile controls were used	–Talc: mean survival, 655 days; no mesotheliomas; injection-site granulomas were common; small pulmonary adenoma in 1 rat, but no other lesions in the lung –Saline: mean survival, 691 days; no mesotheliomas – Chrysotile: mean survival, 598 days; 18 mesotheliomas	80
Intravaginal and perineal							
Talc; composition not provided	Not provided	100 mg in 0.5 mL saline	Sprague-Dawley rats; 7 F	Daily for 3 mo	Talc was administered perineally (in aerosol form) or intravaginally; controls were untreated or given intravaginal administration of saline Baseline cervicovaginal smears were obtained at study initiation; all animals were killed at study termination	–All animals in both test groups developed infection: Intravaginal test group: 5 had vulvovaginitis, 6 had endometritis, 4 had pelvic infection, and 3 had ovary infections (7 ovaries) Perineal group: all had vulvovaginitis, 4 had endometritis, 5 had pelvic infection, 4 had ovarian infection (8 ovaries), 2 developed salpingitis and tubal inclusion Saline controls: 1 had endometritis Untreated controls: 2 had vulvovaginitis and endometritis with infection in both ovaries, and 1 of these animals developed salpingitis –No neoplastic change was found	83

(continued)

Table 5. (continued)

Talc/composition	Particle size	Dose/conc	Animals; #/grp	Dose duration	Procedure	Results	Reference
Intratracheal							
Talc dust from a mill in Vermont; <1% quartz; no fibrous material	MMAD, 7.5 µm; percentage mass <5 µm was 26%	0.15 mL/100 g bw of the dust in 0.9% NaCl containing 13.3 µg/mL rabbit surface active material 0, 0.15, 0.75, or 3.75 mg/100 g bw	Hamsters, 6	Single exposure	The suspension was instilled intratracheally –Dose–response study; results 1 day after exposure –Biochemical and cellular indicators of injury in BAL were measured	–No significant effect on macrophage numbers –PMN numbers were elevated – Lactate dehydrogenase, peroxidase, and albumin levels increased in a dose-dependent manner	218
		3.75 mg talc/100 g bw	Hamsters, 4 (exposure) or 3 (controls)		–Time course experiment; measurements made 1, 4, 7, and 14 days after treatment in bronchoalveolar lavage fluid	–PMN values approached control levels at 4-14 days postexposure –Peroxidase values approached control values by day 7 postexposure – Albumin levels decreased rapidly after exposure – Chronic toxic effects on macrophages were observed	
Intravenous							
Approx 61% SiO_2, 32% MgO, 1% Al_2O_3	<5 µm	25 mg in 0.5 mL physiological saline	Male guinea pigs, 24 test animals, 8 controls	3 doses; given on days 0, 7, and 15	iv injection into the thigh vein in the hind leg; 2 test animals and 1 control were killed at 8 different intervals (from 1 to 150 days) after the last dose	–8 Animals died immediately after the second and third doses –Gross observations: no significant abnormalities in the liver; moderate enlargement of the abdominal lymph nodes at study termination; varying degrees of congestion in the lungs developing early and persisting throughout – Some particles lodged in the alveolar capillaries of the lung; by day 15, many small focal areas of macrophages and lymphocytes developed near the alveolar capillaries, and an increased density of talc particles was seen – Talc particles were observed in the lungs and in the liver throughout the study, and in the abdominal lymph nodes at day 30+; no talc was seen in the tracheobronchial lymph nodes, but a moderate degree of lymphopoiesis was observed at various times	84

Abbreviations: BAL, bronchoalveolar lavage fluid; conc, concentration; F, female; grp, group; iv, intravenous; M, male; MMAD, mass median aerodynamic diameter; MTAC, mean total aerosol concentration; n/a, not applicable; NTP, National Toxicology Program; PMN, polymorphonuclear neutrophils.

is less common. Pure talcosis results in pulmonary function test results that are consistent with restrictive pulmonary disease.

Effects of occupational exposure. Studies examining the pulmonary effects of occupational exposure to talc by talc miners and millers and by workers in industries that use talc are summarized in Table 6. Statistically significantly elevated standardized mortality ratios (SMRs) for silicosis and silico-tuberculosis were observed in an early study of talc miners and millers in the Italian Piedmont region.[92] The miners were employed for at least 1 year and the millers for at least 2 years in their respective occupations. Talc in this region reportedly contained no fibrous material, except for tremolite microinclusions. This study also found statistically significantly reduced SMRs for malignant neoplasms, including lung, bronchial, and tracheal cancers. Updates of this study reported similar results, including statistically significant increases in mortality, which were attributable primarily to nonmalignant respiratory diseases among the miners, no increases in SMRs for cancer, including lung cancer, and no mesothelioma cases.[93,94]

A cohort study of talc miners and millers employed for at least 1 year found no statistically significant SMRs for all causes, all cancers, or diseases of the circulatory system or respiratory tract.[95] These workers were exposed to talc and magnesite-containing trace amounts of quartz, tremolite, and anthophylite. There were no cases with lung cancer or mesothelioma even among the workers in the highest exposure category.

The results of several other epidemiological studies were likely confounded by the presence of up to 3% silica or 6% actinolite in the talc, exposures to high concentrations of silica with or without exposures to fibrous talc or tremolite, or concurrent exposures to radon daughters.[96-102]

A meta-analysis of studies of miners and millers who worked with nonasbestiform talc reported summary SMRs for lung cancer of 0.92 (95% confidence interval [CI]: 0.67-1.25) for millers in 5 countries exposed to high levels of talc without exposure to other occupational carcinogens, and 1.2 (95% CI: 0.86-1.63) for miners in 3 countries exposed to high levels of talc as well as to silica or radon and radon daughters.[28] The corresponding SMRs for death from all causes were 0.95 for the millers and 1.10 for the miners.

Studies examining radiological, lung function, and clinical (eg, wheezing, coughing, bronchitis) parameters in talc miners and millers and rubber workers found some statistically significant decreases in lung function.[97,103-107]

Case Report

A 70-year-old nonsmoking female was determined to have intense endobronchitis and airway stricture following inhalation of large amounts of cosmetic talc.[108] The patient frequently poured a "small pile of talcum powder" into her hand and applied it to her face. Bronchoscopy showed diffuse, severe endobronchitis that extended throughout both main stem bronchi. Chest radiography and computed tomography imaging showed complete collapse of the right upper and middle lobes of the lung; the right lung was normal with the exception of scattered areas of mild bronchial wall thickening, bronchial plugging, and a few nonspecific nodules. Bronchial biopsies showed edema, chronic inflammation, and fibrosis, and there were confluent foreign-body granulomata that contained birefringent crystalline material. Spectral analysis confirmed the crystals were the same composition as the talc used by the patient.

A case of chronic pulmonary granulomatous reaction was reported in a woman who applied "nonpowdering talc" to her face for 20 years, followed by use of talcum powder 2 to 3 times a day during a 10-year period, usually in an unventilated room.[109] The patient had smoked for 20 years. The amount of powder used per year was described as 2 boxes, but the amount per box was not stated. Chest X-rays showed fine diffuse opacities, and anterolateral thoracotomy showed a diffuse nodular consistency. A heavy intraalveolar and interstitial granulomatous inflammation was found at biopsy, and numerous birefringent particles were found inside the giant cells. The foreign body material contained in the granulomas was characteristic of talc. After 2 years of follow-up, a biopsy of an enlarged lymph node showed granulomatous inflammation. It was the opinion of the investigators that this was a case of not true talc pneumoconiosis but chronic sarcoidosis and coincidental talc deposition in the lung.

Pulmonary talcosis was reported in several cases of misuse of talcum powder in which the patients dusted their entire body with large amounts of powder at least once a day.[110,111] including one in which an individual also dusted the bed sheets every day,[112] and in a case in which the powder was purposefully inhaled.[113] A woman who excessively used talc for herself and her children died from rapidly progressive disease and pulmonary hypertension. Cases of accidental inhalation of large amounts of talc by infants and children have been reported, and consequences have ranged from complete recovery to death.[67,114-118] Specifics of these cases are not included because the results are not from normal, intended use of the product. Also not included in this safety assessment are reports of adverse effects due to injection of talc with iv drug abuse.

Reproductive and Developmental Toxicity

Oral

Orally administered talc was not a developmental toxicant in mice, rats, hamsters,[119] or rabbits.[120] Chemical characterization of the talc was not provided in any of these studies.

Groups of 20 to 22 gravid albino CD-1 mice and groups of 20 to 24 gravid Wistar rats were dosed by gavage with 0, 16, 74, 350, or 1600 mg/kg bw talc as an anhydrous corn oil suspension on days 6 to 15 of gestation.[119] Aspirin was used as a positive control in both species. The mice were killed on day 17 and the rats on day 20 of gestation and the number of implantation sites, resorptions sites, and live and dead fetuses, and the live pup body weights were recorded. In both mice and rats, the

Table 6. Pulmonary Effects of Occupational Exposure.[a]

Talc composition and particle size (if given)	Study population and location	Time frame examined	Procedure/parameters measured/limitations	Findings	Reference
Mining and milling –Some chlorite and quartz; very minor to trace amounts of magnesite and dolomite; no amphibole or chrysotile minerals were detected	–1346 millers, 438 miners, and an equal number of age-matched controls from the town of Alba (>1 yr in job) –Mine location: Italy—Germanasca and Chisone Valley (Piedmont)	Employees who began work between 1921-1950—followed until 1974	Historic prospective study – Cumulative exposure for each worker was estimated from the results of successive determinations of air dust content from 1948+ (until retirement or June 30, 1974) – Exposure levels by distribution of total number of inhaled particles (cumulative exposure for each worker was estimated from the results of successive determinations of air dust content and quantified by calculating an appropriate value of the total amount of inhaled particles during the employment period) Miners: Level 1: 566-1699 mppcf/yr (n = 405) Level 2: 1700-5665 mppcf/yr (n = 423) Level 3: 5666-12 750 mppcf/yr (n = 518) Millers: level 1: 25-41 mppcf/yr (n = 163) level 2: 142-424 mppcf/yr (n = 144) level 3: 425-906 mppcf/yr (n = 131) Limitations: – Possible lack of comparability of the occupational and control groups for comparing mortality – Smoking status was not known	–By observed vs expected comparison, the observed overall mortality of miners and millers was significantly lower than expected –There was no relationship found between the ratio of observed to expected deaths and the interval between first exposure and death – Among different exposure classes, the ratio did not increase with increasing exposure For miners: –**Respiratory disease (all except TB; SMR = 1.38), silicosis (SMR = 2.01), and silico-TB (SMR = 1.58) were statistically significantly greater than expected** –Breakout by exposure showed increasing ratios with increased exposure for these diseases – Breakout by interval between first exposure and death showed increasing ratios with increasing latency-years for respiratory diseases (all except TB); it was noted that for silicosis with or without TB, the ratios were unchanged over time because of the absence of pneumoconiosis in controls, but the number of observed cases showed a constant increase with latency – Researchers noted that the trends in dose and latency and the different incidences of silicosis suggests that the inducing factor was silica, not talc –Incidence of malignant neoplasms: – *all malignant neoplasms(SMR = 0.77), of the lungs, bronchus, and trachea (SMR = 0.46), and of other sites (SMR = 0.58) were statistically significantly lower than expected* – breakout by interval between first exposure and death for all malignant neoplasms and lung cancer showed a decrease with increasing latency – an increasing trend was observed for cancer of the larynx – *CV disease was statistically significantly lower than expected (SMR = 0.75)* For millers: –*CV disease was statistically significantly lower than expected (SMR = 0.78)* –There were no consistent trends observed for any cause of death –Breakout by interval between first exposure and death indicated that the ratio of all tumors increased with increasing latency, but the number of observed deaths was still less than expected	92
–Composition as above –Dust counts represented particle sizes of 0.5-5.0 μm	–1260 miners and 418 millers in above study	As above	–Because of the concern stated above, ie, the possible lack of comparability of the occupational and control groups for comparing mortality, expected death rates were recalculated using the death rates of the Italian male population as the standard death rate –The mortality patterns for 1946-1974 were examined using the rates relevant to 1951 for the first 5 yr	Miners: –**The observed cause of death for "all causes" (SMR = 1.25); nonmalignant respiratory diseases (SMR = 3.29; primarily pneumoconiosis), and TB (SMR = 1.98) were statistically significantly increased** –There were 58 cases of pneumoconiosis and 13 cases of TB-associated with pneumoconiosis –An increasing trend with increasing exposure was observed for pneumoconiosis and TB – At the highest exposure level, ~20% of total deaths were due to pneumoconiosis, with or without TB – the researchers stated that the high frequency of pneumoconiosis in miners was attributable to the high content of free silica in the air dust, which was as high as 18% in drilling operations Millers: –**The observed cause of death for "all causes" was statistically significantly increased (SMR = 1.2)** –The observed cause of death was increased but NS for nonmalignant respiratory diseases (SMR = 1.5) and TB (SMR = 2.0) –There were only 3 cases of pneumoconiosis and 1 case of TB-associated with pneumoconiosis – There was no consistent trend with increased exposure level	94

(continued)

Table 6. (continued)

Talc composition and particle size (if given)	Study population and location	Time frame examined	Procedure/parameters measured/limitations	Findings	Reference
–Nonasbestiform talc	–1795 males; 1244 miners and 551 millers (>1 yr employment) –Mine location: Val Chisone, Turin Italy	1946-1995	Update of study described above –Total mortality and selected cause of death; those with a significant increase are given (shown as SMR (95% CI)) –No information was provided on smoking status –Mortality by duration of exposure was examined –Mortality by time since first exposure (latency) was examined	Miners: **All causes: 1.3 (1.2-1.4)** **Oral cavity cancers: 6.1 (3.9-9.1)** **Respiratory tract diseases: 3.1 (2.5-3.7)** **Digestive tract diseases: 1.4 (1.0-1.8)** **Cirrhosis: 1.8 (1.3-2.5)** **–SMR for lung cancer was not significantly increased; 1.1 (0.7-1.5)** Millers: **Oral cavity cancers: 3.3 (1.3-6.9)** **–SMR for lung cancers was 0.7 (0.3-1.2)** –For all miners and millers, no trend in risk with exposure was observed for any of the causes of death –**When miners only were examined, an increasing trend in risk with increasing exposure was observed for nonneoplastic respiratory disease (ie, silicosis); <10 yr exposure, the SMR was 2.8 (1.7-4.6); 10-20 yr exposure, 2.8 (1.7-4.2); >20 yr exposure, 3.2 (2.5-4.1)** For all miners and millers, **a direct trend was observed only for nonneoplastic respiratory disease**; at < 20 yr latency, SMR was 1.5 (0.7-2.6); **20-30 yr, 2.4 (1.5-3.4); >30 yr, 2.4, 1.9-3.0)**	93
–Nonasbestiform talc –Trace amounts of quartz, tremolite, and anthophyllite – Fibers had been detected near the detection limit for optical microscopy	–94 miners (>1 yr employment) 295 millers (>2 yr employment) –Mine located in Norway; the mean value for radon daughter exposure was 3.5 pCi/L at the worksite	1935-1972 (millers) 1944-1972 (miners)	–Levels of dust exposure were not registered during the actual period; samples collected from 1980-1982 demonstrated great variability between job category and workplace: Mill: 1.4-54.1 mg/m^3 Mine: 0.94-97.35 mg/m^3 Limitations: –Numbers were too small for further conclusions on cause-specific mortality or to form inferences on particular cancer types	–For combined miners/millers, SMRs were <1 for all causes, all malignant neoplasms, and diseases of the respiratory system For miners only, obs > exp for number of malignant neoplasms – for combined miners/millers, cancer incidences at all sites, lung, prostate, and intestine, SIRs were <1; SIRs for incidences of kidney, stomach, and bladder cancers were 1.2% (95% CI, 0.1-3.4), 1.1 (95% CI, 0.41-2.15), and 2.1 (95% CI, 0.8-4.3) – for miners only, obs > exp for cancer incidence at all sites, stomach, lung, prostate, and other sites – for millers only, obs > exp for cancer incidence of the bladder	95
–No asbestos in samples –Free silica levels were <0.25% for nearly all bulk talc samples – Free silica detectable only in occasional air samples – Talc shards and ribbons were seen in talc bulk and airborne dust samples – Significant quantities of magnesite, chlorite, and dolomite – Traces of calcite, biotite, ankerite, and phlogopite	–225 millers, 163 miners (all males; 47 were included in both groups; >1 yr employment) –Vermont mines (radon daughter levels ranged from trace quantities to 0.12 working levels; single measurements up to 1.0 working levels have been measured)	1940-1975	–US mortality rates were used; data from 1940-1967 were obtained and deaths after 1967 were extrapolated –However, because Vermont rates (1949-1975) for nonmalignant respiratory diseases and respiratory cancer deaths are greater than US rates, comparisons were made for these causes of deaths with those expected using Vermont rates; cause-specific expected deaths for the study population were obtained by applying death rates, calculated from yearly tallies of deaths and census data, to the person-years of observation of the cohort members Limitations: –Selection bias from radiographic monitoring of talc workers; the bias is most likely small – No data on smoking habits were available	–There were 90 talc-worker deaths observed and 77.32 expected (NS) –For all talc workers, the observed number of deaths for total nonmalignant respiratory disease which was specific for ONMRD, excluding influenza and pneumonia were statistically significantly increased – 9 of the 11 workers with ONMDR had radiographic reading consistent with pneumoconiosis – The possibility of an interactive effect between cigarette smoking and talc exposure was discussed Miners: – **Deaths due to respiratory malignant neoplasms were statistically significantly increased** – This increase was also found using Vermont data Millers: –**Deaths due to total nonmalignant respiratory diseases and ONMRD (7 observed/0.89 expected US) were statistically significantly increased** –This increase was also found using Vermont data –The researchers stated that because excess lung cancer mortality was observed for miner and not millers suggests that additional etiologic agents, alone or in combination with talc dust, affects miners	98

(continued)

Table 6. (continued)

Talc composition and particle size (if given)	Study population and location	Time frame examined	Procedure/parameters measured/limitations	Findings	Reference
–Milled product is a talc-chlorite mixture –Contains 0%-3% quartz	–1070 male workers at a milling site in the French Pyrenees (>1 yr employment) –Local (1968+) and national mortality rates were used for comparison	1945-1994	–A nested case–control study protocol was used –Two case control studies were set up for each cohort: a lung-cancer study and a study of nonmalignant respiratory disease – Occupational histories and smoking information was collected by an external interviewer	–The SMR for all causes of death (1968+) was 0.93 –The SMR for nonmalignant respiratory diseases was 0.27 – The incidence of pneumoconiosis was 0 – The SMR (obs/exp) for all cancers was 0.73, for stomach cancer was 0.40 (0.38-2.75), and for lung cancer was 1.06 (0.43-2.19)	99
–Milled product is talc-chlorite or talc-dolomite Contains 0.5%-4% quartz	–542 male workers from 3 mines and their respective mills in the Styrian Alps (>1 yr employment –Mortality rates of Styria were used for comparison	1972-1995	–Work histories were abstracted from company records; smoking history was obtained from a variety of sources	–The SMR for all causes of death was 0.75 –The SMR for nonmalignant respiratory diseases was 1.06 **The SMR for pneumoconiosis was 5.56 (95% CI; 1.12-16.2); 3 cases were observed** – The SMR for all cancers was 1.02, for stomach cancer was 1.18 (0.38-2.75), and for lung cancer was 1.23 (0.76-1.89)	99
	–Cohort: 40 cases; 39 French and 1 Austrian –44 controls; 41 French and 3 Austrian		Nested case–control study for respiratory disease	Cumulative exposure to talc (yr-mg/m^3): <100; OR = 0.22 100-400; OR = 1.00 400-800; OR = 1.97 ≥800; OR = 2.53 –Mortality increased with exposure **all cases: OR = 1.08 (1.02–1.16)** pneumoconiosis: OR = 1.17 (0.99-1.38) COPD: OR = 1.02 (0.86-1.2)	
	Cohort: 30 cases; 23 French and 7 Austrian –88 controls: 67 French; 21 controls		Nested case control study for lung cancer	Cumulative exposure to talc (yr-mg/m^3): <100; OR = 0.86 100-400; OR = 1.07 400-800; OR = 0.60 ≥800; OR = 0.73 –A relationship between mortality and exposure was not observed	
–Did not contain tremolite; only amphibole mineral was nonasbestiform actinolite (1 bed at ≤6%); ≤42% carbonate minerals, 0.2%-1.6% quartz	–Workers (number not specified) from a company in Russia that mined, ground, and processed talc; total number of cases not stated (>3 yr at plant) –The "other population" were matched noncancer/nonworker deaths from the same town (number not specified)	1949-1975	–Estimated the death rate by relating the number of deaths from cancer of cases to the number of man-years of work for all employees during the same period –The calculated death rates were compared with the analogous death rate for the controls	–**RR of death from tumors of all sites was 5.1 (P < 0.001) for males and 6.4 (P < 0.001) for females** –**RR of death from lung cancer was 4.5 (P < 0.02) for males** and 9.3 (NS) for females –For lung cancer of male workers compared to controls, the death rate of those <59 yr old was 2× greater, of those 60-69 yr old was 6.51× greater, and of those **70+ yr old was 40.02× greater** –**RR of death from gastric cancer was 3.7 (P < 0.02) for males and 6.3 (P < 0.05) for females**	96
–Minimal amounts of crystalline silica and asbestiform minerals –Contained chlorites and carbonates	–7 miners/millers –8 adult age matched by decade male controls – Vermont mines	4-27 yr of exposure (time frame not stated)	–Lifetime exposure to talc ranges from 12 to 5930 mppcf –Pulmonary tissue from deceased talc workers was examined and compared to pulmonary tissue of controls	–Lungs of 4 workers exposed for 4-19 yr exhibited **focal and diffuse fibrosis with accumulations of talc**, but chest X-rays were negative for pneumoconiosis –Lungs of 3 workers exposed for 19, 26, and 27 yr had **areas of diffuse confluent fibrosis and talc** – 2 workers exposed for 27 yr had positive chest X-rays; the chest X-ray was not available for the remaining worker – Extensive pulmonary fibrosis was found in the patient exposed for 27 yr (5930 mppcf); large amounts of silicon and aluminum were found in the lungs – The severity of lesions and the concentrations of magnesium and silicon in the lungs compared top controls increased with duration of exposure – Circumscribed granulomas were not observed	100

(continued)

Table 6. (continued)

Talc composition and particle size (if given)	Study population and location	Time frame examined	Procedure/parameters measured/limitations	Findings	Reference
–Talc was essentially free from silica and asbestos –Geometric mean exposure was 1.8 mg/m^3 respirable dust	–116 miners and millers older than the age of 25 in 3 Vermont plants –Avg years Employed was 8.5	1975-1976	–Exposure levels were >3.0 mg/m^3 respirable dust –A medical history, including questions pertinent to the respiratory system, and smoking history were obtained – Pulmonary function tests were performed – An appropriate control group was not available; observed values were compared to predicted values from a standard pop –Chest X-rays were taken in 100 of the patients Limitations: – The follow-up interval is short and the overall range of exposures within the study may be too narrow to detect exposure-related effects in the small study pop – Effects on pulmonary function in nonsmokers were not associated with lifetime or current talc exposure after a relatively short avg years. Employed; longer follow-up would be needed before concluding there is no effect of talc on nonsmokers at this exposure level	–**Observed/predicted FEV$_1$ (FEV%) and MMEF (MMEF%) were significantly reduced** –Years of employment and talc-years (ie, lifetime dust exposure) were significantly associated with decreased FEV$_1$/FVC and MMEF%, but not with FVC% or FEV% –A 43.3% prevalence of any chest X-ray abnormality was observed; with a third being diffuse parenchymal opacities or pleural abnormalities – 12 patients had small round opacities and 9 had small irregular opacities; there was a statistically significant association with talc-years	105
–Contained talc, chlorite, and a small quantity of dolomite –0.5%-3% free silica (<1% particle size distribution <10 µm) –Does not contain asbestos	–176 millers from Luzenac, France (cross-sectional study)	1978	–Cross-sectional study	–46 workers (27%) had pneumoconiosis –36 of the cases were slight –10 of the cases had higher profusion or large opacities – Intensity and duration of dust exposure were linked to radiologic signs of pneumoconiosis	97
	–Dust exposed workers –Local and national pop were used as controls	1945-1981	–Retrospective study, completed by a prospective study until 1988	–Difference in life expectancy of dust-exposed workers compared to the local and national pop was NS –Differences in mortality due to cancer, including lung and digestive system cancers, were NS –In a cohort or workers deceased between 1970 and 1981 compared to 97 age-matched controls, the mortality ratio for chronic respiratory diseases was 2.4; a follow-up in 1998 confirmed these results	
	–39 pneumoconiotic workers; 6 had profusion equal to 2 or 3 –39 matched for smoking and age nondust-exposed controls		–Respiratory function was compared	–VC, TLC, and single breath TCO were statistically significant decreased in patients with pneumoconiosis compared to controls	
	–8 hospitalized pneumoconiotic workers		–A bronchoalveolar lavage was performed	–Hypercellularity was observed, with a significant increase in neutrophilic and eosinophilic PMN leukocytes –Numerous talc particles were found in all lavage fluids, including uncoated plate-like particles (0.5-40 µm) and atypical ferruginous bodies)	

(continued)

Table 6. (continued)

Talc composition and particle size (if given)	Study population and location	Time frame examined	Procedure/parameters measured/limitations	Findings	Reference
3 Mines: –MT: free silica content was below the limit of detection (<0.8%); no fibers; NC: 1.5% free silica; acicular particles (aspect ratios 5-100:1 and some diameters <0.1 μm); TX: 2.2% free silica; tremolite and antigorite fibers (0.5-3 μm in length) –Geometric mean concentrations of respirable dust in samples (mg/m^3) for miners and millers was 0.66 and 1.1 (MT), 0.45 and 1.56 (TX), 0.14 and 0.26 (NC)	–177 talc workers from MT, 71 from TX, 51 from NC –Since there were no differences among regions by age, smoking, or exposure groups, the populations were combined –Were compared to 1140 blue collar workers (males and females from NC in electronics, synthetic textiles, bakeries, and bottling plants)	Avg from 3 plants: 5.5 (TX), 6.6 (MT), and 10.1 (NC) yrs (time frame not stated)	–Cumulative exposure (mg/m^3 × yr) was 1.21 for MT, 2.64 for TX, and 0.28 for NC –All workers completed a respiratory questionnaire –Chest X-rays were taken and sputum was collected Limitations: – Workers examined were only those currently working – Length of the working history was a relatively short time for the development of occupationally related symptoms – Estimating past exposure was a problem	Prevalence of dyspnea: –6% in nonsmokers, 10% in exsmokers, 3% in smokers; 5% total (prevalence was increased with age; no demonstrated association with cumulative exposure) Prevalence of pleural thickening: – 0% in nonsmokers; 4% in exsmokers; 9% in smokers; 5% total (tendency to increase with age; no demonstrated association with cumulative exposure) – Cumulative exposure was not significant for any of the lung function tests Parameters examined and compared to blue-collar controls: – Cough: 20.3% of test vs 16.7% controls – Phlegm: 20.3% of test vs 17.3% of controls – Dyspnea: 5.8% of test vs 7.5% of controls – Bilateral pleural thickening: 6.3% of test vs 0.4% of controls Mean percentage of predicted pulmonary function compared to 292 controls: FEV_1: 99.7 FVC: 101.0 Peak flow: 97.9 FEF_{50}: 94.1 FEF_{75}: 84.5	104
–Nonasbestiform talc-chlorite mixture	–398 patients from talc facilities in the Styrian alps, Austria, and in the French Pyrenees, France –>5 yr continuous employment between 1989 and 2001	1988-2003	–In the French mill, overall exposure decreased from a geometric mean exposure of 1.95 mg/m^3 (GSD3.9) in 1986 to 0.80 mg/m^3 (GSD 4.3) in 2003; the high GSDs are due to different exposures based on job –In the Austrian mill, the 1988-1995 geometric mean exposure was 0.75 mg/m^3 (GSD 3.67); in 1996, it was 0.30 mg/m^3 (GSD 3.25) –Lung function parameters were measured, with the following confounders: pack-years; apparatus used to determined respiratory function; gender; gender-specific age and height; medical histories – Regression coefficients (95% CI) are presented Limitations: – The symptoms questionnaire was only used a mean of 2 times at the French site and less at the Austrian site – The mean duration of follow-up was <5 yr –Prevalence of self-declared respiratory symptoms, including the following confounders: pack-years of cigarettes for chronic bronchitis and usual cough and/or phlegm and age for dyspnea –ORs (95% CI) are presented	Total cumulative exposure per 10 yr mg/m^3: FEV_1 (mL): −6.58 (−13.81-0.65) FVC (mL): −7.71 (−15.45-0.03) FEV_1/FVC (%): 0.000 (−0.090-0.090) Cumulative exposure at inclusion per 10 yr mg/m^3: FEV_1 (mL): −7.26 (−14.65-0.13) FVC (mL): −8.47 (−16.38 to −0.57) FEV_1/FVC (%): −0.004 (−0.096-0.087) Cumulative exposure since inclusion per 10 yr mg/m^3: FEV_1 (mL): 7.75 (−25.49-40.99) FVC (mL): 10.24 (−28.22-48.70) FEV_1/FVC (%): 0.105 (−0.364-0.574) Total cumulative exposure per 10 yr mg/m^3: Chronic bronchitis: 1.014 (0.963-1.068) usual cough or phlegm: 1.021 (0.993-1.050) Dyspnea: 1.040 (0.997-1.087) Cumulative exposure at inclusion per 10 yr mg/m^3: Chronic bronchitis: 1.032 (0.985-1.081) usual cough or phlegm: 1.014 (0.983-1.046) Dyspnea: 1.031 (0.985-1.080) Cumulative exposure since inclusion per 10 yr mg/m^3: Chronic bronchitis: 0.473 (0.193-1.158) usual cough or phlegm: 1.250 (0.986-1.584) Dyspnea: 1.405 (0.870-2.257)	107

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Table 6. (continued)

Talc composition and particle size (if given)	Study population and location	Time frame examined	Procedure/parameters measured/limitations	Findings	Reference
			Radiograph results were examined –ORs (95% CI) are presented –Profusion: using the standard X-rays, the profusion (concentration) of small opacities is classified on a 4-point major category scale (0, 1, 2, or 3), with each major category divided into 3, giving 12 ordered subcategories of increasing profusion; category 0 refers to the absence of small opacity and category 3 represents the most profuse	Initial cumulative exposure per 10 yr mg/m^3: Profusion >0/1: 1.056 (1.031-1.085) Profusion ≥1/0: 1.060 (1.028-1.095) Pleural abnormalities: 1.036 (0.960-1.119) Cumulative exposure since inclusion per 10 yr mg/m^3: Profusion ≥0/1: 0.917 (0.838-1.004) Profusion ≥1/0: 0.858 (1.028-1.095) Pleural abnormalities: 1.145 (0.980-1.336)	
The talc ore contained chlorite, aluminum, some dolomite (<3%), some quartz (<3%), and traces of calcite, apatite, pyrite, and mica –Amphiboles were not detected	–166 millers (158 M/8 F) from a talc-producing factory in SW France	Workers employed 1989-1990	–Geometric mean exposure at the time of the study was 1.87 mg/m^3 (GSD, 2.5 mg/m^3) –Each patient was given a standardized questionnaire and questioned about smoking and occupational history during their annual medical check-up –A chest radiograph that had been taken between 1982 and 1987 was reviewed – 139 patients had a second radiograph in 1992 – The prevalence of self-reported symptoms (as %) according to cumulative exposure were determined Limitations: – Less than optimal quality of the spirometric tests that led to the exclusion of 30 patients	<20 yr mg/m^3 (n = 46): Chronic bronchitis: 0% Chronic cough or phlegm: 8.7% Dyspnea: 4.4% Wheeze: 4.4% 20-50 yr mg/m^3 (n = 25): Chronic bronchitis: 4% Chronic cough or phlegm: 20% Dyspnea: 8% Wheeze: 4% 50-150 yr mg/m^3 (n = 54): Chronic bronchitis: 13% Chronic cough or phlegm: 35.7% Dyspnea: 17% Wheeze: 3.7% >150 yr mg/m^3 (n = 41): Chronic bronchitis: 2% Chronic cough or phlegm: 14.6% Dyspnea: 14.6% Wheeze: 0%	106
			–Standardized functional variables according to cumulative exposure were determined	<20 yr mg/m^3 (as mean [SD]; n = 36): FVC: 1.33 (1.28) FEV: 1.22 (1.21) FEV/FVC: 0.25 (0.70) MMEF: 0.66 (1.58) 20-50 yr mg/m^3 (n = 20): FVC: 0.82 (1.04) FEV: 0.77 (1.22) FEV/FVC: 0.27 (0.79) MMEF: 0.36 (1.41) 50-150 yr mg/m^3 (n = 44): FVC: 1.10 (1.07) FEV: 0.74 (1.17) FEV/FVC: −0.04 (0.80) MMEF: −0.19 (1.15) >150 yr mg/m^3 (as mean [SD]; n = 36): FVC: 0.65 (1.03) FEV: 0.50 (1.06) FEV/FVC: 0.24 (0.75) MMEF: −0.06 (1.12)	

(continued)

Table 6. (continued)

Talc composition and particle size (if given)	Study population and location	Time frame examined	Procedure/parameters measured/limitations	Findings	Reference
			–Radiological opacities at the first radiograph –Given in terms of cumulative exposure to talc	Any opacity including 0/1: Coefficient: 0.33 OR (95% CI): **1.39 (1.06-1.84)** Any opacity excluding 0/1: Coefficient: 0.97 OR: **2.65 (1.25-5.64)** –4 pleural abnormalities were reported at the first reading –The prevalence of small opacities was higher in the second radiograph, with 11 new opacities compatible with pneumoconiosis (1/0 or above)	
Plant workers Rubber workers Nonfibrous talc; <2 fibers/cm^3 –<1% free silica –Avg dust entilatoron ranged from 0.47-3.55 mg/m^3, with most jobs exposed to <1 mg/m^3	–80 talc workers (15.9 yr avg length of employment) and 189 nonexposed rubber workers (13.4 yr avg length of employment) (Average talc exposure, ie, "dust years", was 9 yr) –Plant location not specified	1972-1974	–Patients were asked about medical, occupational, smoking, and respiratory histories –Pulmonary function tests were performed –Exposure to talc was evaluated by respirable mass sampling – 28 workers were studied for acute change in $FEV_{1.0}$ and FVC for 1 shift – Pulmonary function changes related to talc exposure were measured in white workers >24 yr old –Chest X-rays were taken in most exposed workers	–There were no significant differences between exposed and nonexposed workers in age, smoking, or socioeconomic or ethnic factors –Statistically significant increases in cough for 3 mo and phlegm for 3 mo (chronic bronchitis symptoms) and wheezing most days and nights (an obstructive respiratory disease symptom) were observed in exposed workers; none of the workers had dyspnea –Talc had no acute effect on entilator capacity – Talc workers had lower (NS) FVC standardized flow rates and a lower ratio of $FEV_{1.0}$ to FVC; the flow rate/FVC at 12.5% FVC was statistically significantly decreased in exposed workers –For workers of >10 yr, residual $FEV_{1.0}$ was statistically significantly decreased in exposed workers – None of the chest X-rays were definitely consistent with classical talc pneumoconiosis	103
Pottery plant workers Nonfibrous talc	–White men from 3 ceramic plumbing fixture plants (>1 yr employment)	Employed during 1939-1966	–Workers were exposed to both silica and talc –Mortality from 1940-1980 was examined Limitations: –Information on smoking patterns was not available	–With high silica/nonfibrous talc exposure, there was a statistically significant increase in SMR for lung cancer (SMR = 2.54) and nonmalignant disease mortality (SMR = 2.20) –With high silica/no talc exposure, the increase was only seen for nonmalignant respiratory disease (SMR = 2.64) –**With nonfibrous talc, SMRs for lung cancer were statistically significant increased with 5-14 and 15+ yr duration of exposure and –14 and 15+ yr since first talc exposure** – SMRs for nonmalignant respiratory diseases were statistically significant increased with <5, but not 5-14 or 15+ yr duration of exposure and with 5-14, but not >15, yr since first talc exposure – **The researchers postulated that nonfibrous talc was related to excess lung cancer, and that it was possible that silica might act as a cofactor or promoting agent**	101,102

Abbreviations: CI, confidence interval; CV, cardiovascular; exp, expected; FEF, forced expiratory flow; FEV, forced expiratory volume; FVC, forced vital capacity; GI, gastrointestinal; GSD, geometric standard deviation; MMEF, maximum midexpiratory flow; NS, nonstatistically significant; obs, observed; ONMRD, other nonmalignant respiratory disease; OR, odds ratio; PMN, polymorphonuclear cells; pop, population; RR, relative risk; SD, standard deviation; SIR, standardized incidence ratio; SMR, standardized mortality ratio; TB, tuberculosis; TCO, transfer factor for carbon monoxide; VC, vital capacity
[a]Bolded text was used to highlight statistically significant increases. Italicized text was used to highlight statistically significant decreases

administration of up to 1600 mg/kg bw talc in corn oil had no effect on reproductive or developmental parameters and had no effect on maternal or fetal survival.

In hamsters, groups of 20 to 23 gravid female golden hamsters were dosed by gavage with 0, 12, 56, 260, or 1200 mg/kg bw talc as an anhydrous corn oil suspension on days 6 to 10 of gestation.[119] The animals were killed on day 14 of gestation and examined as described previously. The administration of up to 1200 mg/kg bw talc in corn oil had no reproductive or developmental effects and had no effect on maternal or fetal survival.

Groups of 12 to 15 gravid Dutch-belted female rabbits were dosed orally with 9, 42, 195, or 900 mg/kg bw talc in corn oil on days 6 to 18 of gestation.[120] Eight gravid negative controls were given only vehicle and 9 gravid positive controls were dosed with 2.5 mg/kg bw of 6-aminonicotinamide on day 9 of gestation. The dams were killed on day 29 of gestation. A total of 1/8, 4/15, 2/12, 5/15, and 2/13 dams of the negative control, 9, 42, 195, and 900 mg/kg bw dose groups, respectively, died or aborted before day 29 of gestation, and the number of live litters for these groups was 6/7, 10/11, 8/10, 10/10, and 7/11, respectively. The researchers concluded that administration of up to 900 mg/kg bw talc on days 6 to 18 of gestation "had no discernible effect on nidation or on maternal or fetal survival." The researchers also stated the number of abnormalities did not differ between test and control animals.

In a dominant-lethal study, groups of 10 male rats were dosed by gavage with a single dose or once daily for 5 days with 30, 300, 3000, or 5000 mg/kg bw talc.[66] Saline was used as the negative control and 0.1 μg/mL triethyl melamine (ip) was the positive control. (The results of the reproductive portion of the study are presented here; the genotoxicity results are presented in that section of the safety assessment). Each treated rat was mated with 2 previously unmated females, and 2 weeks after mating, the female rats were killed and the effects on fertility and preimplantation loss were determined. In the single-dose study, significant dose-related decreases in average corpora lutea and preimplantation losses were reported in the test groups at weeks 4 and 5. In the repeated dose study, significant increases in average implantations and corpora lutea were reported in the test groups at week 6, as were significant differences in the proportions of females with 1+ or 2+ dead implants. However, the results observed at the highest dose did not vary significantly from the negative control, and no dose–response or time-trend patterns were indicated.

Genotoxicity

In Vitro

Talc was not genotoxic in an unscheduled DNA synthesis (UDS) assay or a sister chromatid exchange (SCE) assay in rat pleural mesothelial cells (RPMCs).[121,122] Three samples of European talc (French, Italian, and Spanish talc) were tested. The samples, which contained 90% to 95% talc with chlorite and dolomite, were asbestos free, and the mean particle size of the samples ranged from 2.6 μm (Spanish and French talc) to 4.0 μm (Italian talc). In the UDS assay, the cells were treated with 0, 10, 20, or 50 μg/cm^2 of each sample of talc for 24 hours. A negative reference particle control, anatase, and 2 positive controls reference particles, Rhodesian chrysotile and crocidolite, were used, and the mean particle sizes of the 3 talc samples were 0.7, 3.2, and 3.1 μm, respectively. The particles were dispersed in culture medium at a concentration of 560 μg/mL by sonication. None of the talc samples enhanced UDS. The negative and positive particles yielded the expected results.

In the SCE assay, RPMCs were treated with 0, 2, 5, 10, and 15 μg/cm^2 of each talc sample for 48 hours. Two negative reference particle controls, anatase and attapulgite, and the 2 positive control reference particles named previously were used, as were the chemical controls mitomycin C in water and K_2CrO_4 in culture medium. Talc did not cause a statistically significant increase in SCEs and was not clastogenic. The negative particle controls and chemical controls gave expected results; chrysotile and crocidolite statistically significantly increased SCEs in 2/4 and 3/8 experiments, respectively.

In Vitro/In Vivo

Talc was not genotoxic in a host-mediated assay or cytogenetic assay. (Chemical characterization data were not provided in either assay). In the host-mediated assay, male ICR mice served as the host and groups of 10 animals were dosed by gavage with a single dose or once daily for 5 days with 30, 300, 3000, or 5000 mg/kg bw talc.[66] *Salmonella typhimurium* TA1530 and G46 and *Saccharomyces cerevisiae* D3 were the indicator organisms. Saline was the negative control and 100 mg/kg bw dimethyl nitrosamine and intramuscular (im) administration of 350 mg/kg bw ethyl methane sulfonate were the positive controls. For comparison, a microdrop of solution, 0.01 to 0.25 mL, of talc was evaluated in an Ames test using *S typhimurium* TA1530 and G46 and *S cerevisiae* D3. Talc caused no significant increase in mutant or recombinant frequencies in the host-mediated assay, and it was not mutagenic in the Ames test.

Groups of 15 male albino rats were given a single dose by gavage and groups of 5 rats were dosed once daily for 5 days with 30, 300, 3000, or 5000 mg/kg bw talc in the cytogenetics assay.[66] Saline was used as the negative control and 0.3 mg/kg bw triethyl melamine (ip) was used as the positive control. The concentrations used during the in vitro aspect of the study were 2, 20, and 200 μg/mL in human embryonic lung culture (WI-38) cells. Talc produced no significant aberrations during the in vivo or in vitro phase and was not genotoxic.

In Vivo

Talc was not genotoxic in a rat dominant lethal assay.[66] (Chemical characterization data were not provided). Groups of 10 male rats were dosed by gavage with a single dose or once daily for 5 days with 30, 300, 3000, or 5000 mg/kg bw talc. Saline was used as the negative control and 0.1 μg/mL triethyl

melamine (ip) was used as the positive control. There were no dose–response or time-trend patterns; talc did not induce dominant lethal mutations in this assay.

Carcinogenicity

In 2010, the IARC Working Group published the monograph stating that there is *limited evidence* in experimental animals for the carcinogenicity of talc not containing asbestos or asbestiform fibers.[18] The Working Group reviewed studies in which talc of different grades was tested for carcinogenicity in mice by inhalation exposure or intrathoracic, ip, or sc injection, in rats by inhalation exposure or intrathoracic or ip injection, oral administration, or intrapleural or ovarian implantation, and in hamsters by inhalation exposure or intratracheal injection.

For humans, the evaluation of the IARC Working Group was that perineal use of talc-based body powder is *possibly carcinogenic to humans (Group 2B)*, and that inhaled talc not containing asbestos or asbestiform fibers is *not classifiable as to its carcinogenicity (Group 3)*.[18] In evaluating the carcinogenicity of talc in humans, the Working Group reviewed cohort studies of talc miners and millers, cohort and case-controlled studies examining the association of cosmetic talc use and the risk of ovarian cancer in humans, and the animal data and evidence regarding the potential mechanisms through which talc might cause cancer in humans. The Working Group found there is *inadequate evidence* in humans for the carcinogenicity of inhaled talc not containing asbestos or asbestiform fibers, and there is *limited evidence* in humans for the carcinogenicity of perineal use of talc-based body powder.

The references cited by the IARC in their review were obtained by the CIR and are cited as appropriate in this safety assessment.

Inhalation

Exposure of hamsters to talc via inhalation did not produce carcinogenic effects.[82] Groups of 50 male and 50 female Syrian golden hamsters were exposed for 30 or 150 min/d, 5 days/wk, to 27.4 $\pm$ 3.4 μg/L mean total aerosol concentration commercial baby powder (95%, w/w platy talc with trace quantities of carbonates and platy chlorite and rutile) until natural death, or, for a maximum of 300 days. A group of 25 male and 25 female hamsters served as the control group. A single-tier exposure was used. There was no statistically significant difference in survival time among groups, but there was a significant difference between males and females within all groups. No clinical signs of toxicity to talc were observed. The type, incidence, and severity of lesions indicated no trend toward a dose–response and no statistically significant differences between exposed and control groups. The incidence of focal alveolar cell hyperplasia (25% in treated groups and 10% in controls) appeared to be affected by treatment, but a 2-way weighted analysis showed no significant association.

A bioassay using mice and rats was performed by the NTP to determine the carcinogenic potential of nonasbestiform, cosmetic-grade talc following exposure by inhalation.[10] There was *no evidence of carcinogenic activity* in male or female B6C3F$_1$ mice, *some evidence of carcinogenic activity* in male F344/rats, and *clear evidence of carcinogenic activity* in female F344/N rats. The talc used was asbestos free and virtually silica-free microtalc; scanning electron microprobe analysis of one lot of talc indicated that 1/1466 particles examined were silica, 136/1466 particles tremolite, and 1241/1466 particles were talc. More than 75% of the particles were in the 1.0 to 3.0 μm range. This study is discussed in greater detail subsequently

A 2-year study was performed in mice: groups of 50 male and 50 female B6C3F$_1$ mice (7 weeks old) were exposed to target concentrations of 0, 6, or 18 mg/m^3 talc for 6 h/d, 5 days/wk, for 103 to 104 weeks. The concentrations were selected based on the results of a 4-week inhalation study in B6C3F$_1$ mice, and that study is presented in Table 5. These exposure concentrations provided a dose equivalent of 0, 2, or 6 mg/kg bw/d for male mice, respectively, and 0, 1.3, or 3.9 mg/kg bw/d for female mice, respectively. The mass median aerodynamic diameter (MMAD) was 3.3 $\pm$ 1.9 μm in the 6 mg/m^3 chamber and 3.6 $\pm$ 2.0 μm in the 18 mg/m^3 chamber. Groups of 40 male and 40 female mice were similarly exposed and killed at 6, 12, and 18 months for interim microscopic evaluations. Some problems were experienced in maintaining control of the chamber concentrations, and there was a 12-week period beginning at week 70 during which the chamber concentrations were substantially lower than the target concentrations. Mean body weights were similar for test and control animals, and there were no clinical findings attributable to talc exposure.

Compared to the 6-month value, the lung talc burden (normalized to control lung wt) was statistically significantly increased at 24 months in 6 mg/m^3 males, at 12 and 24 months in 18 mg/m^3 males, at 18 and 24 months in 6 mg/m^3 females, and at 12, 18, and 24 months in 18 mg/m^3 females. When lung talc burdens were normalized to exposure concentration, a statistically significant difference was observed between the 6 and 18 mg/m^3 males at 12 and 24 months but not at 6 and 18 months. The mouse lung talc burdens are provided in Table 7.

Changes in enzymatic activities in bronchoalveolar lavage fluid were noted mostly in the 18 mg/m^3 males and females; measured enzymatic activity was increased in the high-dose animals at 18 and 24 months. A statistically significant increase in β-glucuronidase activity was seen at 12 months in the high-dose animals, and at 24 months, the activity was increased in all test groups. Lavage fluid polymorphonuclear cells were statistically significantly increased in males and females of the 18 mg/m^3 group at all times except at 12 months; statistically significant increases were observed in some 6 mg/m^3 interim groups. The population of bronchoalveolar lavage fluid macrophages was significantly decreased in the female test groups at 24 months. The phagocytic activity of the macrophages recovered from the lavage fluid at 12, 18, and 24 months was statistically significantly decreased by exposure to 18 mg/m^3 talc. At 24 months, there was no effect on the viability of the macrophages. Lung tissue collagen and proteinase activity were

Table 7. Lung Talc Burden in Mice.[10,a]

	Male		Female	
Evaluation	6 mg/m^3	18 mg/m^3	6 mg/m^3	18 mg/m^3
Normalized to control lung weight (mg talc/g control lung), mo				
6	0.415 0.114 (2)	1.41 ± 0.29 (4)	0.524 ± 0.056 (4)	1.35 ± 0.24 (4)
12	1.084 ± 0.130 (4)	9.00 ± 1.45^b (4)	0.707 ± 0.170 (4)	6.17 ± 1.39^b (4)
18	0.426 ± 0.040 (2)	8.36 (n = 1; no std dev calc)	1.387 ± 0.178^c (4)	7.83 ± 1.36^b (3)
24	2.973 ± 0.762^b (8)	19.73 ± 4.03^c (6)	2.667 ± 0.720^c (6)	20.05 ± 0.98^c (5)
Normalized to exposure concentration (mg talc/g control lung per mg talc/m^3), mo				
6	0.069 ± 0.019 (2)	0.078 ± 0.016 (4)	0.087 ± 0.009 (4)	0.075 ± 0.013 (4)
12	0.181 ± 0.022 (4)	0.500 ± 0.081^d (4)	0.118 ± 0.028 (4)	0.343 ± 0.077^d (4)
18	0.071 ± 0.007 (2)	0.464 (n = 1; no std dev calc)	0.231 ± 0.030 (4)	0.435 ± 0.075 (3)
24	0.496 ± 0.127 (8)	1.096 ± 0.224^d (6)	0.445 ± 0.120 (6)	1.114 ± 0.055^d (5)

Abbreviation: std dev, standard deviation.
[a](n) number of animals examined for lung talc burden.
[b]Significantly different ($P \leq 0.05$) from the 6-month group.
[c]Significantly different ($P \leq 0.01$) from the 6-month group.
[d]Significantly different ($P \leq 0.05$) from the 6 mg/m^3 group.

significantly increased in exposed male and female mice. At 24 months, collagen and lung fluid collagenous peptides were statistically significantly increased in the 18 mg/m^3 group, and most proteinase activity was increased as well.

Chronic active inflammation without alveolar epithelium hyperplasia, squamous metaplasia, or interstitial fibrosis was reported in exposed mice. An accumulation of macrophages was observed in the lungs, and talc-containing macrophages were found in the bronchial lymph nodes. The incidence of pulmonary neoplasms was similar for test and control animals. In the upper respiratory tract, cytoplasmic eosinophilic droplets in the nasal mucosal epithelium occurred and were concentration dependent. There was *no evidence of carcinogenic activity* in male or female B6C3F$_1$ mice exposed to talc.

A lifetime study was performed in rats; groups of 50 male and 50 female F344/N rats (6-7 weeks old) were exposed to the same dosing regimen and target concentrations of talc as mice until mortality reached 80% in any exposure group, that is, males were exposed for 113 weeks and females for 122 weeks. (The concentrations selected were based on the results of a 4-week inhalation study in F344/N rats and that study is described in Table 5). The MMAD was 2.7 ± 1.9 μm in the 6 mg/m^3 chamber and 3.2 ± 1.9 μm in the 18 mg/m^3 chamber. As with the mice, there was difficulty in maintaining the chamber concentrations for the rats; there was a 7-week period beginning at week 11 during which time the concentration for the 18 mg/m^3 group varied from 30 to 40 mg/m^3 and there was a 12-week period beginning at week 70 during which the chamber concentrations were substantially lower than the target concentrations for both groups. Groups of 22 male and 22 female rats were exposed similarly and killed at 6, 11, 18, and 24 months for interim evaluations. Survival was similar for test and control animals. Body weights of the low-dose animals were similar to controls and final body weights of the high-dose animals were slightly (14%) lower than controls. Compared to controls, the absolute and relative lung weights in high-dose males were statistically significantly increased at 6, 11, 18 months, and at study termination; in high-dose females at 11, 18, 24 months, and at study termination; and in low-dose females at 18 months and study termination.

A concentration-related impairment of respiratory function was observed in exposed male and female rats, and the severity increased with increasing duration of exposure. In the 6 and 18 mg/m^3 males and in the 6 mg/m^3 females, the lung talc burden (normalized to control lung wt) was statistically significantly increased at 11, 18, and 24 months compared to the 6-month value. In the 18 mg/m^3 females, the 18- and 24-month values were statistically significantly increased compared to the 6-month values. When lung talc burdens were normalized to exposure concentration, a statistically significant difference was observed between the 6 and 18 mg/m^3 males at 6 and 11 months but not at 18 and 24 months. At 24 months, the lung talc burden (normalized to exposure concentration) was higher in the 6 mg/m^3 males than in the 18 mg/m^3 males. In the females, the only statistically significantly difference between the low- and high-dose groups was at 6 months. The interim rat lung talc burdens are provided in Table 8.

Pulmonary function was impaired (ie, restricted) in a concentration-related manner, increasing in severity with exposure duration. After 24 months of exposure, changes in enzymatic activities in bronchoalveolar lavage fluid were noted compared to controls; statistically significant increases in β-glucuronidase were seen in all test animals. Also, lavage fluid polymorphonuclear cells were statistically significantly increased and macrophage cells were statistically significantly decreased in all test animals; a statistically significant increase in lymphocyte cell populations was reported in all test group females. The viability and phagocytic activity of the macrophages recovered from the lavage fluid were not affected by exposure to talc. Lung tissue collagen and proteinase activity were significantly increased in exposed male and female rats.

Table 8. Lung Talc Burden in Rats.[10,a]

	Male		Female	
Interim evaluation	6 mg/m^3	18 mg/m^3	6 mg/m^3	18 mg/m^3
Normalized to control lung weight (mg talc/g control lung), mo				
6	2.63 ± 0.24 (3)	10.83 ± 0.23 (3)	2.43 ± 0.19 (3)	8.34 ± 0.12 (3)
11	4.38 ± 0.59[b] (3)	20.96 ± 2.04[b] (3)	4.71 ± 0.26[b] (3)	14.16 ± 3.36 (3)
18	7.31 ± 0.71[c] (3)	27.57 ± 0.91[b] (3)	7.66 ± 0.34[c] (2)	24.33 ± 0.63[b] (3)
24	10.45 ± 1.26[c] (6)	24.15 ± 3.41[b] (9)	9.10 ± 0.88[c] (2)	29.40 ± 2.40[c] (3)
Normalized to exposure concentration (mg talc/g control lung per mg talc/m^3), mo				
6	0.439 ± 0.040 (3)	0.602 ± 0.013[d] (3)	0.406 ± 0.032 (3)	0.464 ± 0.007[d] (3)
11	0.731 ± 0.098 (3)	1.165 ± 0.113[d] (3)	0.785 ± 0.043 (3)	0.787 ± 0.187 (3)
18	1.22 ± 0.12 (3)	1.53 ± 0.05 (3)	1.28 ± 0.06 (2)	1.35 ± 0.04 (3)
24	1.74 ± 0.21 (6)	1.34 ± 0.19 (9)	1.52 ± 0.15 (2)	1.63 ± 0.13 (3)

[a](n) number of animals examined for lung talc burden.
[b]Significantly different ($P \leq 0.05$) from the 6-month group.
[c]Significantly different ($P \leq 0.01$) from the 6-month group.
[d]Significantly different ($P \leq 0.05$) from the 6 mg/m^3 group.

Granulomatous inflammation occurred in the lungs of most test animals, and severity increased with duration and concentration. Hyperplasia of the alveolar epithelium and focal interstitial fibrosis were statistically significantly increased at study termination; squamous metaplasia of the alveolar epithelium and squamous cysts were significantly increased in the 18 mg/m^3 females only. Talc-containing macrophages were reported in the peribronchial lymphoid tissue of the lung and in the bronchial and mediastinal lymph nodes. In the full study, the incidences of pulmonary neoplasms in male rats of the test group were similar to controls. However, in female rats of the 18 mg/m^3 group, the incidences of alveolar/bronchiolar adenoma, carcinoma, and adenoma/carcinoma (combined) were statistically significantly greater than controls; 1 squamous cell carcinoma was reported in this group. In the upper respiratory tract, hyperplasia of the respiratory epithelium of the nasal mucosa was observed in male test animals and accumulation of cytoplasmic eosinophilic droplets in the nasal mucosal epithelium was observed in males and female test animals; the incidence of these lesions was concentration dependent. Benign, malignant, or complex (combined) adrenal medulla pheochromocytomas occurred with a significant positive trend in male and female rats, and the incidences in the 18 mg/m^3 group were statistically significantly increased compared to controls. The incidence of adrenal medulla hyperplasia was statistically significantly decreased in exposed males, but not exposed females, compared to controls. It was concluded that there was *some evidence of carcinogenic activity* of talc in male F344/rats based on an increased incidence of benign or malignant pheochromocytomas of the adrenal gland and *clear evidence of carcinogenic activity* of talc in female F344/N rats based on increased incidences of alveolar/bronchiolar adenomas and carcinomas of the lung and benign or malignant pheochromocytomas of the adrenal gland.

Responses to/reviews of the NTP inhalation bioassay

- One member of the NTP Board of Scientific Counselors, Technical Reports Review Subcommittee, voted against the NTP conclusions on the carcinogenic potential of nonfibrous talc in rats.[123] This board member asserted that talc-induced lung tumors occurred only in the group of animals that experienced the most chronic toxicity and inflammation, and that the lung toxicity data were presented as an empirical observation rather than related to the risk assessment implications of the bioassay. Additionally, it was the opinion of the board member that the evaluation of the pheochromocytomas was inadequate because the spontaneous incidence of this tumor in rats was not sufficiently addressed and that the incidence of pheochromocytomas was not treatment related.
- At a talc workshop that was cosponsored by the FDA, CTFA, and ISRTP, a unanimous consensus was reached regarding the NTP talc bioassay.[11] It was the opinion of the Panel at the workshop that "because of the extreme doses and the unrealistic particle sizes of the talc that was used, because of the negative results in mice and male rats, because of the lack of tumor excess at the low doses, and because of the clear biochemical and cytological markers of excessive toxicity in the female rats, the positive talc bioassay results in female F344/N rats were the likely experimental artifacts and nonspecific generic response of a dust overload of the lungs and not a reflection of a direct activity of talc. Given the gross differences of rodent and human lungs, the lung clearance capabilities of humans, and the possible conditions of customary human exposures, the NTP bioassay results in F344/N female rats cannot be considered as relevant predictors of human risk."
- A critical appraisal of the NTP study discussed test concentration selection and the effect of lung particle overload.[124] The appraisal noted that a 4-week study, rather than a subchronic study, was used to determine the test concentrations used in the bioassay; additionally, only 2 test concentrations were used and exposure at these concentrations impaired lung clearance in the 4-week

study. The appraisal cited a recommendation that, instead, the long-term bioassay should be performed using 3 concentrations and that only the highest concentration tested should show interference with lung defense mechanisms, and the 2 lower concentrations should not interfere with clearance and particle accumulation. It was the opinion of this appraisal that lung particle clearance in both rats and mice was impaired, resulting in altered accumulation kinetics, with long-term exposure at concentrations of 6 and 18 mg/m^3. Therefore, the maximum tolerated dose (MTD) was exceeded at both exposure concentrations, and because the MTD was exceeded, "classification of such particles with respect to human pulmonary carcinogenicity should be considered carefully." Finally, the appraisal stated that the NTP conclusion of clear carcinogenicity in female rats should be qualified by a statement indicating that the lung tumors that occurred were mostly likely produced secondary to particle overload and related chronic toxicity.

- The human exposure to respirable talc particles during normal product use (values obtained from studies by Russell et al[56] and/or Aylott et al[54]) was compared to the exposure of rats and mice in the NTP study.[26] According to these researchers, based upon the determinations reported in the literature, human exposure to respirable talc particles during normal product use is approximately 2000 to 20 000 times lower than that used for rats and mice in the NTP study.
- The International Life Sciences Institute convened the Workshop on Relevance of the Rat Lung Response to Particle Overload for Human Risk Assessment.[125] The workshop addressed studies reporting lung tumors in rats resulting from chronic inhalation of poorly soluble, nonfibrous particles (PSPs) that are of low acute toxicity and not directly genotoxic, including nonasbestiform talc. The workshop noted that PSP-induced tumors in rats are associated with the following sequence of responses: particle accumulation, chronic active inflammation, epithelial cell hyperplasia, and metaplasia; the chronic active inflammation is associated with the emergence of neoplastic cells. It was stated that, although for direct-acting mutagens the rat appears to be a good qualitative predictor of the human lung cancer, for PSPs it appears to be more sensitive than humans and other rodent species at doses and exposure intervals that result in particle overload in the rat lung. However, because it is not known whether high lung burdens of PSPs can lead to lung cancer in humans via mechanisms similar to those in rats, "it was the consensus view of the workshop that there are insufficient data at present to conclude that the PSP-induced tumor response in the rat model is not relevant for human hazard identification. In other words, in the absence of mechanistic data to the contrary, it must be assumed that the rat model of tumorigenicity can identify potential carcinogenic hazards to humans."
- Another comment paper discussed the use of micronized talc in the NTP study, which resulted in a significantly reduced particle size compared to cosmetic talc, that is, 2.7 to 3.2 μm instead of 6.0 to 6.9 μm.[126] The commenter stated that the use of micronized talc significantly affected the bronchopulmonary deposition and clearance characteristics of the inhaled aerosol; the micronized talc particles were deposited deeper in the lung where clearance depended on alveolar macrophages, whereas cosmetic talc particles would have deposited in the ciliated portion of the respiratory tract. The commenter also remarked on the difficulty in controlling aerosol concentrations and that the 7-week period in which the rats were exposed to twice the intended aerosol concentration most likely aggravated an existing overload condition.

Parenteral

Intrapleural. Talc did not induce pleural tumors in rats following intrapleural injection.[121] A group of 35 Sprague-Dawley rats were given an intrapleural injection of 20 mg talc (mean size 2.6 ± 2.3 μm; no other chemical characteristics provided), and control groups were given an intrapleural injection of saline (40 rats) or no injection (38 rats). The animals were killed when moribund. No pleural tumors were observed in the test or control group. As a comparison, the researchers examined the effect of Canadian chrysotile (90% of the fibers were <8 μm in length) in 39 rats and found that 25.6% of the rats developed mesothelioma.

Intratracheal. Groups of 24 male and 24 female Syrian golden hamsters were dosed weekly with intratracheal instillations of 0 or 3 mg talc in 0.2 mL saline for 18 weeks.[8] The chemical composition of talc was 61% to 63% silicon dioxide, 32% to 34% magnesium dioxide, and 0.85% to 1.06% other dusts; the particle size distribution was 93% <25 μm, 86% <16 μm, 54% <10 μm, 26% <5 μm, and 2% <1 μm. An untreated control group was also included. The animals were allowed to live until natural death or until killed when moribund. Animals given talc had a shorter lifespan (46 weeks) when compared to the saline controls (55 weeks). The talc-treated animals showed signs of minor respiratory disorders during treatment, and at necropsy, microscopic examination revealed pulmonary congestion and interstitial fibrosis, but no detectable dust deposits, granulomas, or mesothelial proliferations. There were 3 tumor-bearing animals; no tumors were in the respiratory tract, although 3 benign lung lesions (mucoepidermoid lesions) were reported. Two forestomach papillomas, 1 thyroid adenoma, and 1 adrenal adenoma were also found.

In a lifetime study, groups of 48 Syrian golden hamsters were dosed once weekly with intratracheal instillations of 3 mg talc.[9] The talc was defined as USP grade and contained 64% to 66% SiO_2, 34% to 36% MgO_2, and <1% other dusts.

Dust-laden macrophages and an accumulation of interstitial cells were observed in the talc-treated animals. A proliferation of fibrillar material, primarily elastic fibers, and multinucleated giant cells with foreign material were observed in the alveolar and interstitial spaces, and occasional accumulation of proteinaceous exudate was seen in the alveoli. No increase in collagen fibers or granulomas was observed. The severity of premalignant lesions was evaluated in the tracheobronchial and alveolar zone of the animals. No dysplasia was observed with talc in either zone. Slight metaplasia and moderate epithelial destruction were observed in the tracheobronchial zone. Moderate hyperplasia was observed in the alveolar zone. The number of lesions induced by talc was not given.

Both intratracheal studies also examined the effects of administering 3 mg talc + 3 mg B[a]P in 0.2 mL saline to hamsters for the 18-week period[8] or for a lifetime.[9] Although the researchers reported that results of the study indicated that talc + B[a]P had a co-carcinogenic effect, the Expert Panel noted that appropriate controls were not used.

Intraperitoneal. Forty 6-week-old Swiss albino mice were given an ip injection of 20 mg of ultraviolet (UV)-sterilized commercial talc (composition not stated) in 1 mL saline, and the animals were observed until there were obvious signs of a tumor or spontaneous death.[127] Fifty-five control animals were injected with 1 mL physiological saline. Animals that died before 9 months elapsed were not included. Twenty-four treated mice were included in the results. Three (12.5%) developed mesothelioma, and no lymphomas were reported. Forty-six the control animals were included in the results; 3 mesotheliomas and 1 lymphoma developed (8.7% total tumors).

Forty Wistar rats were given weekly ip injections of 25 mg talc suspended in 2 mL saline weekly for 4 weeks, and the animals were allowed to live until natural death.[128] It is stated that the talc was composed of magnesium silicate but no other components are given, and the particle size was not known. Eighty control animals were injected with saline only. Few tumors developed in the test animals, and; the tumor rate was 2.5%. The time to first tumor was 587 days. No tumors were reported in the control animals.

Ovarian Cancer Risk

Particulate migration in the genital tract. Migration of particles through the female genital tract has been examined as a possible explanation of the presence of talc in the ovaries. However, at the "Talc: Consumer Uses and Health Perspectives" workshop, it was stated that "available histologic and physiologic studies provide no basis to conclude that talc can migrate to the ovaries from the perineal region."[11] Because of the discussion on whether or not translocation is a viable theory in general, several studies on the transport of particulate matter other than talc are briefly summarized subsequently, and mixed results were found. Studies specifically relating to talc migration then follow.

Nonhuman. No translocation of bone black (ie, carbon black) from the vagina to the oviducts was found in monkeys.[129] Cynomolgus monkeys were restrained so that their pelvis was elevated, and 0.3 mL of a suspension of 4% bone black in 30% dextran was placed in the vaginal posterior fornix of 4 monkeys and 0.3 mL of a suspension of 4% bone black in physiological saline containing carboxymethyl cellulose (CMC) was placed in the vaginal posterior fornix of 1 monkey. Ten units of oxytocin were administered by im injection at the same time. The monkeys were released after 20 minutes. One hour after deposition of the bone black, 2 monkeys that received suspensions in dextran and the one that received the saline with CMC suspension were anesthetized and the reproductive tract of each animal was removed; the oviducts were flushed. The remaining 2 monkeys were processed in the same manner 72 hours after deposition. The test samples, the solutions without bone black (negative controls), and samples with a suspension of bone black (positive control) were filtered with Millipore membrane filters (0.45 μm). Particles resembling bone black were found on filters used for oviduct flushing solutions as well as the solution blanks; the numbers ranged from very few to occasional on all filters and no distinct differences in numbers or shape of these particles were apparent. The new filter blank that was examined immediately upon removal was the only sample on which no bone black particles were found. The researchers stated that these results suggest that there was no translocation of bone black from the vagina to the oviducts.

Twenty-six New Zealand white rabbits were used to examine whether starch particles migrate from the vagina to the peritoneal cavity.[130] Anesthetized rabbits were divided into an untreated control group, a group given 50 mg of a glove lubricant powder intravaginally, and a group given 50 mg of the lubricant powder and *Chlamydia trachomatis* (an inclusion former). Ovulation was then induced in all groups. After 1 to 4, 17, and 25 days, the rabbits were anesthetized and the peritoneal cavity was rinsed; the lavage fluids were analyzed for starch particles. Small numbers of starch particles were found on all slides. Retrograde migration was found after 3 days. The number of small particles between the treated and control groups was not statistically significantly different. Large starch particles were statistically more numerous in the 2 test groups compared to the controls.

Human. Sterile carbon particles were suspended in 30% dextran and 3 to 4 mL of the suspension was deposited into the posterior fornix of 3 women placed in the lithotomy position (ie, head tilted downward at a 15° angle from horizontal) that were undergoing abdominal surgery; 1 mL (10 U) of oxytocin given simultaneously via im injection.[131] During surgery, 20 to 34 minutes after deposition of the particles, the Fallopian tubes were sutured 1 cm lateral to the uterus, excised, and then flushed with saline. Carbon particles were found in the rinsate from 2 of the 3 patients. In a study using India ink, it was found that India ink (0.2 mL) that was injected into the uterine cavity 15 minutes to 24 hours prior to abdominal surgery was transferred to the Fallopian tubes in 27 of 50 women in the

proliferative phase and in 23 of 35 women in the secretory phase of the menstrual cycle.[132] Injection of ink into the cervical canal often resulted in immediate back flow into the vagina; the ink reached the Fallopian tubes in 17 of 56 women. However, when the ink was placed into the vagina, the ink was transferred to the Fallopian tubes in only 1 of 18 women in the proliferative phase in 12 to 24 hours. The ink was found to pass from the vagina to the uterus in 2 of 37 women; one of these woman where the ink was transferred had a lacerated cervix. (In this study, some of the women had received an im injection of 2 units of oxytocin at the same time the ink was administered, but it did not appear to affect the results, and the women were placed in the Trendelenburg position after the abdomen had been opened.)

In a study using a radionuclide procedure, the migration of a particulate radioactive tracer from the vagina to the peritoneal cavity and ovaries was determined in 24 women scheduled to undergo gynecological surgery.[133] The day prior to surgery, the women were placed in a supine position, and less than 3 mL of 10 to 15 mCi [^{99m}Tc]-labeled human albumin microspheres with a size range of 30 to 50 μm were deposited in the posterior fornix. Each patient remained in a supine position for 24 hours. The radionuclide material remained in place for 21 women, and in 16 of these women, "sufficiently high radioactivity levels" were determined as evidence of migration to the uterus or the Fallopian tubes and ovaries. In 14 of the 21 patients, radioactivity was measured in adnexa separately from the uterus. Nine of the 14 patients had "marked" radioactivity in the tubes and ovaries; the 5 patients that did not had severe tubal occlusions. Another group of researchers stated that this finding may be misleading because only 1 radioactive label was used.[129]

The migration of starch particles from powdered gloves was examined in groups of female patients who were undergoing abdominal surgery.[134] A group of 17 females was examined with powdered gloves 1 day prior to surgery and a group of 12 females was examined with powdered gloves 4 days prior to surgery. Corresponding control groups of 15 and 14 females, respectively, were examined with powder-free gloves. Peritoneal fluid was collected during surgery. The number of starch particles found in patients examined with powered gloves 1 day prior to surgery was statistically significantly increased for both small and large particles at all locations of the genital tract and for large particles in the peritoneal fluid. No particles were found in 2 patients examined with powdered gloves and a few particles were found in 3 patients examined with powder-free gloves 1 day prior to surgery. In patients examined with powdered gloves 4 days prior to surgery, there were statistically significantly more small and large starch particles in the cervix and uterus, but not in the Fallopian tubes or peritoneal fluid, compared to patients examined with powder-free gloves.

A catheter was used to apply 1 to 2 mL of 10 ± 2 MBq-TC-99m-labeled macroaggregates of human serum albumin, 5 to 20 Hm in size, into the posterior vaginal fornix of 1000 women with primary or secondary infertility in the follicular phase of the menstrual cycle; 15 women were examined during the early to midluteal phase.[135] The women were in a supine position, and hysterosalpingoscintigraphy (HSS) scans (a method to evaluate the transport function of uterus and Fallopian tubes) were obtained immediately and at various intervals for 4 hours after application. Labeled particles were detected in the uterus at the time of the first HSS scan of every woman examined, and women in both the follicular and luteal phases were examined. In women in the follicular phase, radioactivity entered the Fallopian tubes on both in 15% of the patients and on one side in 64% of the patients; significant radioactivity entered the pelvis of 6% of the patients. Radioactivity was not found to migrate to the Fallopian tubes of the remaining women that were in the follicular phase or in any of the women examined during the luteal phase.

Talc migration in the genital tract

Nonhuman. Particles of talc were identified in the ovaries of rats that received intrauterine instillations of talc.[136] In a pilot study, one group of 4 female exbreeder Sprague-Dawley rats received 1 intrauterine instillation of 100 mg/mL talc in 250 μL PBS; these rats were killed 5 days after dosing. A second group of 4 rats received intrauterine instillations of the talc suspension on days 0, 6, and 15; 2 animals were killed on day 20. (Spectral analysis reported a 3:1 ratio of silicon to magnesium; it is not stated whether the talc was nonfibrous). The remaining 2 animals were dosed again on days 22 and 30 and killed on day 49. The ovaries of each animal were analyzed by an ashing procedure.

Two groups of 12 female exbreeder Sprague-Dawley rats were then dosed intravaginally with 250 μL of the same talc suspension or PBS only, and 2 animals per group were killed 24 hours, 48 hours, or 4 days after dosing. Their ovaries were removed and analyzed as mentioned earlier. Particles of talc were found in the ovaries of the 2 rats of the talc group that were killed after 4 days but not in those killed at 24 or 48 hours or in the PBS-treated animals.

Radioactivity was not found in the ovaries of rabbits dosed intravaginally with talc.[64] Three female large white rabbits received a single intravaginal instillation of 0.5 mL of [^{3}H]talc administered as a suspension in aq glycerol jelly solution (10 mg/mL; 1 μCi/mL) and 3 were given 6 daily doses of the talc suspension. (Chemical characterization data were not provided). In the single-dose rabbits, urine was collected every 24 hours for 3 days; the animals were then killed, the urogenital tract was dissected out, and the total radioactivity was determined in the urine, ovaries, Fallopian/uterine tubes and cervix, the bladder, and the vagina. In the urogenital tract 72 hours after dosing, radioactivity (0.004% of the dose) was only detected at the site of administration. (The limit of detection was 0.25 μg). Total recovery was not quantitated.

In the multiple-dose group, the rabbits were killed 72 hours after the final dose; radioactivity was determined as described for the single-dose animals. In the urogenital tract at 72 hours after the final dose, 0.035% of the radioactivity was found at the site of administration and 0.006% was found associated with the cervix and Fallopian/uterine tubes. No radioactivity was found in the ovaries.

Talc was not found to translocate from the vaginas of female cynomolgus moneys to the ovaries.[129] A pilot study was first performed with 2 female cynomolgus monkeys. Talc samples were exposed to a calculated neutron fluency of 1.2×10^{17} n/cm^2, and 125 mg neutron-activated talc suspended in 0.3 mL deionized water containing 1% CMC was placed into the vaginal posterior fornix of each monkey. (Deposition was similar to that of bone black, described previously). Three days after talc deposition, the animals were anesthetized and peritoneal lavage was performed; when the peritoneal cavity was opened to collect the fluid, the lavage was repeated through the abdominal incision. Peritoneal lavage was also performed on a control animal. Radionuclide activity was determined with ^{46}Sc, ^{59}Fe, and ^{60}Co. There was no measurable translocation of activated talc from the site of deposition to the uterine cavity, oviducts, ovaries, or peritoneal cavity. (The vagina and the cervix were analyzed together). It appeared that detectable amounts of ^{60}Co were found in a portion of the oviducts of each test animal, but this was not supported by ^{46}Sc or ^{59}Fe data. Approximately 0.3 and 2.3 mg talc were found in the vaginas of the 2 test monkeys 3 days after instillation.

In the definitive study, 6 monkeys were dosed with a neutron-activated purified blend of cosmetic talc for 30 consecutive workdays.[137] The animals were restrained and dosed as defined in the pilot study; additionally, 10 units of oxytocin were administered by im injection once weekly. ^{46}Sc, ^{59}Fe, ^{60}Co, and ^{61}Cr were used as tracers. The peritoneal lavage was performed as above 2 days after the last talc deposition. Measurable quantities of talc were observed in the vagina + cervix sample, and the quantities ranged from 0.006 to 117 mg talc. (The researchers theorized that the wide variations were most likely due to different menstrual cycle phases). No measurable levels of talc ($> \sim 0.5$ µg) were present in the samples from the peritoneal lavage fluid, ovaries, oviducts, or body of the uterus.

Human. Talc particles were found in approximately 75% (10 of 13) of the ovarian tumors and 50% (12 of 21) of the cervical tumors during an extraction–replication technique used to examine tissue from patients with ovarian or cervical cancer.[138] (The technique involved replicating embedded tissue using a polyvinyl alcohol solution, tape stripping the replicated tissue, and using an AEI-6B electron microscope to examine the replicas.) The particles found in the ovarian tumors were located deep within the tumor tissue and were not universally dispersed; some of the particles were 1000 Å but most ranged from 1000 Å to 2 µm. The particles found in the cervical tumor tissue were generally larger than those in the ovarian tumors; some crystals were as large as 5 µm. Additionally, many particles of talc were found concentrated in the deeper layers of a primary carcinoma of the endometrium; however, talc was not found in a secondary tumor in the ovary of the same patient. Talc particles were also found in 5 of 12 normal ovarian tissue samples removed from patients with breast cancer. (Chemical characterization data were not provided for the talc that was found; the researchers noted that no asbestos fibers were found in any of the tissues studied.)

In 100 consecutive cases of women operated on for pelvic disease at Johns Hopkins Hospital, a total of 175 normal ovaries were removed and examined for particulate matter.[139] Seventy-two cases were classified as having laminated calcifications referred to as psammoma bodies. Six examples of crystalline foreign bodies were found and examined by scanning electron microscopy, and computer-assisted microscopic X-ray analysis was used to determine the elemental composition of the foreign bodies in 4 cases. The particles were composed primarily of magnesium and silicon; the researchers stated that in industrial North America, the most common compounds containing magnesium and silicate are talc and asbestos. Nine percent of the patients appeared to have magnesium silicate granulomas in their normal ovaries, and an additional 9% contained very similar histologic entities.

The ovaries of 24 women with benign ovarian neoplasms who were undergoing surgery at Columbia Presbyterian Medical Center between 1992 and 1993 were examined for the presence of talc using both light and electron microscopy.[140] Twelve women reported talc application directly to the perineum or underwear, and 12 women were age-matched controls. The mean number of lifetime exposures for women reporting talc use was 14 820, with a range of 4784 to 39 312 lifetime exposures. The ovaries of 2 stillborn fetuses were analyzed as negative controls; no talc was found in these ovaries. Sections of normal ovary from the 12 women who reported the talc use were analyzed. A linear relationship between ovarian talc particle burden and exposure was not found. Neither light nor electron microscopy values correlated with perineal talc usage. Electron microscopy counts were 0 for about half of the patients exposed to talc as well as half of the controls; talc was observed with light microscopy in all patients exposed to talc and 11 of 12 controls. There was a negative correlation between the values obtained by light microscopy and electron microscopy. The mean electron microscopic particle count was higher in those exposed to talc and the mean light microscopic particle count was higher in the women who did not report talc use. In 1 patient for which both ovaries were analyzed, both talc counts varied greatly between the right and left sides (0 vs 1 669 000 particles/g wet tissue wt by electron microscopy and 556 vs 6 particles by light microscopy, respectively). Asbestos was detected in the ovaries of 4 talc-exposed patients and 5 of the control patients.

The pelvic lymph nodes of a woman with stage III ovarian papillary serous carcinoma, with metastatic serous carcinoma in 2 of the 6 right external iliac and obturator nodes, were examined using polarized light microscopy and scanning electron microscopy and X-ray spectroscopy.[141] The patient applied talc daily for 30 years to the perineum and also applied it to underwear and sanitary napkins. She had 3 term deliveries, followed by a tubal ligation and she did not smoke, use oral contraceptives, or, with the exception of 6 months of progesterone therapy, use postmenopausal hormone therapy. Birefringence was seen using polarized light; 3 of the 4 nodes that did not contain metastases displayed polarizing material. Examination of lymph nodes by combined scanning electron microscopy

and X-ray spectroscopy revealed plate-like particulates in the 5 to 10 μm range within the lymph nodes; the energy dispersive X-ray spectroscopy showed a magnesium and silicate signature that was compatible with talc. Nodes from 12 other patients were examined; this case was strongest for birefringence. (Electron microscopy or X-ray spectroscopy had not been performed).

Epidemiological studies. Numerous epidemiological studies have been performed examining the risk of ovarian cancer following talc exposure.[142-174] These studies are summarized in Table 9. There is a large amount of information presented in these studies, and a variety of parameters were examined. Table 10 is a summary of the relative risk (RR) for ovarian cancer presented in case–control studies; this table only includes those studies that indicated "ever" use of talc in the perineal area, independent of the manner of use.[143-146,148,149,152-155,157,159,161-163,165-167,170,173,174]

Analysis of Ovarian Cancer Risk in the Epidemiological Studies

Concerns about cosmetic talc are based on reports suggesting that talc may migrate from the perineum to the ovaries and epidemiological studies suggesting a weak but fairly consistent association between perineal dusting and ovarian cancers.[12]

The possibility that using cosmetic talc powder can cause ovarian cancer was suggested when talc particles were found in or on human ovarian tissues.[131-133,138,175,176] The translocation of talc particles from the perineum to the ovaries would require that these particles pass from the perineum through the vagina and cervical canal, move across the uterus and against the ciliary motion of the Fallopian tubes, cross the peritoneal space between the fimbriae and ovaries, escape phagocytosis in the peritoneal space, and attach to the surface of the ovaries to accumulate in the ovaries.[177,178]

However, there is evidence that talc particles found in ovaries are attributable to sample contamination, rather than to particle translocation.[12,179] This view is supported by studies finding talc in 100% of women with no known talc exposure, for example, as well as in 85% of women reporting frequent perineal talc applications.[140]

Further, many translocation studies have been criticized for using particles with only a single radionuclide[133] because the radiolabel leaches from such particles, leading to the untenable assumption that the leached radioactive marker represents translocated particles.[12,62,137,179-185] In a study conducted to help address this issue, ^{46}Sc, ^{60}Co, ^{59}Fe, and ^{51}Cr served as tracers in 125 mg neutron-activated talc deposited intravaginally 30 times over 45 days to ensure exposure through at least 1 menstrual cycle in cynomolgus monkeys.[12,137,179,182] The tracers were not detected in the uterus, Fallopian tubes, ovaries, or peritoneal lavage fluid 2 days after the 30th talc application.

The migration of many different types of materials from the vagina through the cervix has been demonstrated in patients in a supine or in the Trendelenburg position or with a lacerated or a dilated cervix. In addition, retrograde menstrual flow is a well-known phenomenon that could help explain the movement of particles to the ovaries in some cases. However, the findings of at least 1 study[132] has been interpreted as demonstrating the formidable barrier that the cervix presents to the translocation of particles from the vagina to the ovaries.[182,186]

Many women may have been exposed to talc in infancy.[140] Infants are typically placed in a supine position and their legs separated during diapering, which could facilitate the passage of talc into the vagina. This may help explain the ubiquitous presence of talc in ovarian tissue. However, it has not been determined whether the hymen blocks exposure to the infant genital tract, or otherwise to what extent, if any, talc can enter the genital tract during diapering.[22]

Several epidemiological studies suggested that medical procedures that would be expected to prevent the translocation of talc to the ovaries, such as tubal ligation or hysterectomy, reduce the RRs estimated for talc use.[148,154,172,187] However, in one of these studies, women who were exposed to talc for 1 to 9 years before tubal ligation or hysterectomy appeared to have an increased risk of ovarian cancer but not in women who had talc exposure for 10 or more years before their surgery.[172] Other studies found no difference in RR between women who had tubal ligation or hysterectomy and women who did not have these procedures.[143,173] One study reported inverse exposure-effect trends with duration of talc exposure after adjusting for tubal ligation.[165] Thus, the literature provides no clear, convincing support for the hypothesis that procedures that would preclude the passage of talc particles from the perineum to the ovaries reduce the risk of ovarian cancer.

The use of talc-dusted condoms or diaphragms, which would clearly result in exposure close to the cervical opening, was not associated with an increased RR estimate for ovarian cancer.[146,148,167] A meta-analysis found no association between talc-dusted diaphragm use and ovarian cancer risk. Overall, these studies do not support the hypothesis that talc can migrate from the perineum or the vagina to the ovaries.

Numerous case–control studies have reported small increases in RR estimates of all ovarian cancers combined in women using cosmetic talc products compared to women with minimal or no exposure, including population-based and hospital-based case–control studies (Tables 9 and 10; Figure 2). Other investigations found no statistically significant increase in risk estimates for ovarian cancer (all subtypes combined), including many case–control studies and 1 prospective cohort study.[151] Presumably the patients in all of these studies used products that contained cosmetic grade talc but information on fibrous content is generally lacking.

Some studies found statistically significant associations between talc use and invasive cancer[143,148,151] while another study reported an association only between talc use and tumors of low malignant potential.[154] Some studies found no statistically significant associations with all subtypes of ovarian cancer considered together but reported statistically significant associations only with specific subtypes of ovarian cancer or endometrioid tumors.[145,148,151,154]

Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk.[a]

Talc/composition	Population/geographical area	Study/diagnosis years	Study description and limitations	Findings	OR or RR (95% CI)	Reference
Ovarian cancer Personal use Prospective study						
Talc; purity and composition not specified	–307 Registered nurses in 11 states with epithelial ovarian cancer (of 31 789 patients of 121 700 total pop that reported using talc; Nurses' Health Study)	1982-1996	–Patients answered questionnaires every 2 yr from 1976 to 1996, patients were questioned about talc use in 1982 –Risk was age adjusted and multivariate for age, parity, OC use, BMI, tubal ligation history, smoking status, and PMH use –Women who did not respond to the questions on talc use in 1982 and who reported a diagnosis of cancer before 1982 were excluded Limitations: – Question of talc use was ever/never only; did not determine the age at which use began or the duration – This also may have contributed to a higher prevalence of use compared to other studies – Were unable to assess the potential effect of talc use prior to first pregnancy – Follow-up period may have been inadequate if latency is >15 yr – Question about tubal ligation was asked as a component of contraceptive use, so not all women may have responded	Ever/never perineal use of talc: 58.3% of cases never used perineal talc – 41.7% of cases ever had perineal use of talc (age) (multivariate) Frequency of perineal talc use: – 60.6% of cases never used talc on perineum – 14% of cases used talc on perineum <1×/wk (age) (multivariate) – 9.8% of cases used talc on perineum 1-6×/wk (age) (multivariate) – 15.6% of cases used talc on perineum daily (age) (multivariate) Talc use on sanitary napkins: – 78.8% of cases never used talc on sanitary napkins – 11.7% of cases used talc on sanitary napkins (age) (multivariate) Talc use perineally and/or on sanitary napkins: – 58.3% of cases did not use talc perineally or on sanitary napkins – 33.6% of cases talc on perineum or sanitary napkins (age) (multivariate) – 8.1% of cases talc on perineum and sanitary napkins (age) (multivariate)	**RR** 1.0 1.05 (0.84-1.32) 1.09 (0.86-1.0) 1.0 1.1 (0.79-1.53) 1.14 (0.81-1.59) 0.95 (0.65-1.4) 0.99 (0.67-1.46) 1.09 (0.79-1.49) 1.12 (0.82-1.55) 1.0 0.89 (0.62-1.29) 0.89 (0.61-1.28) 1.0 1.11 (0.87-1.41) 1.15 (0.9-1.46) 0.89 (0.58-1.35) 0.9 (0.59-1.37)	151
			–The tumors were stratified by histological subtype –Risk was adjusted for age or for age, parity, OC use, and tubal ligation, and sometimes for BMI (multivariate)	All serous cancers (185 total): –54.6% never used talc perineally – 45.4% ever used talc perineally (age) (multivariate) Serous invasive cancers (160 total): – 52.5% never used use talc perineally – 47.5% ever used talc perineally (age) (multivariate) Endometroid cancers (42 total): – 61.9% never used use talc perineally – 38.1% ever used talc perineally (age) (multivariate) Mucinous cancers (50 total): – 60% never used use talc perineally – 40% ever used talc perineally (age) (multivariate)	**RR** 1.0 1.23 (0.02-1.64) 1.26 (0.94-1.69) 1.0 1.33 (0.98-1.82) **1.40 (1.02-1.91)** 1.0 0.91 (0.49-1.69) 0.91 (0.49-1.87) 1.0 0.98 (0.56-1.73) 0.93 (0.53-1.66)	
Hospital-based cases/hospital-based controls						
Talc; purity and composition not specified	–135 women in the Washington, DC area with epithelial ovarian cancer (hospital based) –171 hospital controls	1974-1977	–Patients were asked questions about reproductive and sexual history, medical history, drug use, other exposures, and talc use Limitation –A potential bias is that talc exposure was not a major focus of the study during questioning	Ever/never talc use: – 45.9% of cases and 35.7% of controls had no exposure to talc – 49.7% of cases and 58.5% of controls had exposure to talc Use with diaphragm: – 18.5% of cases and 24% of controls reported diaphragm use with talc – 10.4% of cases and 6.4% of controls reported diaphragm use with no talc Areas of application of talc – 57% of cases and 49.1% of controls reported no body talc use – 40% of cases and 45.6% of controls reported some body talc use – 27.4% of cases and 33.3% of controls reported all-over use of talc – 5.2% of cases and 1.8% of controls reported genital use of talc	**RR** 1 0.7 (0.4-1.1) 0.8 (0.4-1.4) 1.6 (0.7-3.7) 1.0 0.8 (0.5-1.2) 0.7 (0.4-1.2) 2.5 (0.7-10.0)	155

(continued)

Table 9. (continued)

Talc/composition	Population/geographical area	Study/diagnosis years	Study description and limitations	Findings	OR or RR (95% CI)	Reference
Talc; purity and composition not specified	–235 females in London and Oxford, England with epithelial ovarian cancer (from 15 hospitals) –451 age-matched hospital controls	October 1978–February 1983	–Patients were asked about talc reproductive and sexual history, contraceptive use, breastfeeding, talc usage, hysterectomy, HRT –All risk estimates were adjusted for age and social class; some were adjusted for parity	Frequency of talc usage: Never: 37.3% of cases; 39.5% of controls Rarely: 2.6% of cases; 3.5% of controls Monthly: 3.0% of cases; 5.3% of controls Weekly: 24.3% of cases; 17% of controls Daily: 30.2% of cases; 30.8% of controls –No consistent trend of increase risk with increasing frequency of talc (χ^2 (trend) = 3.80; $P = 0.05$)	**RR** 1.0 0.9 (0.3-2.4) 0.7 (0.3-1.8) 2.0 (0.3-3.4; $P = 0.07$) 1.3 (0.8-1.9)	142
Talc; purity and composition not specified	–77 patient at Johns Hopkins Hospital in Baltimore, MD with epithelial ovarian cancer –46 age–race-matched hospital controls	1981-1985	–Patients questioned about presence and length of genital fiber and respiratory fiber exposure (in this study, fiber exposure was defined as exposure to asbestos, talc, and fiberglass), reproductive factors, estrogen use, family history of cancer, and contraceptive use; information on previous abdominal and gynecological operations was ascertained –Potential confounders: obesity, socioeconomic status, religion, reproductive status, live births >2, OC use; confounders added dependent on effect on OR	Areas of application of talc: –88% of cases and 87% of controls reported genital fiber use –28.9% of cases and 18.6% of controls reported genital bath talc exposure –61.8% of cases and 55.8% of controls reported application of bath talc to body (risk adjusted for # of live births) – 50.7% of cases and 54.5% of controls reported cosmetic face powder use (risk adjusted years of education) Use of talc on sanitary napkins or on diaphragm: – 61.8% of cases and 55.8% of controls reported talc use on sanitary napkins (risk adjusted for highest wt 1 yr prior to diagnosis) – 18.9% of cases and 11.4% of controls reported powder on diaphragm (risk adjusted for # of live births and years of education)	**OR** 1.0 (0.2-4.0) 1.7 (0.7-3.9) 1.6 (0.6-2.7) 1.1 (0.4-2.7) **4.8 (1.3-17.8)** 3.0 (0.8-10.8)	167
Talc; purity and composition not specified	–499 patients at Roswell Park Cancer Institute, Buffalo, NY, with epithelial ovarian cancer –755 age-at-diagnosis matched hospital controls – Numbers were adjusted based on the answers to questionnaires (ie, if the patient did not respond to talc use or recall the duration of use)	October 1982–October 1995	–Information on parity, menstrual history, use of exogenous hormones, contraceptive history, talc use, and personal hygiene was obtained and patients were questioned about medical, social, family, dietary, and occupational histories –Risk was adjusted for OC use, smoking history, family history of epithelial ovarian cancer, age at menarche, menopausal status, income, education, geographic location, history of tubal ligation and/or hysterectomy Limitations: – Ascertainment and recall bias likely – Patients were asked whether condoms or diaphragms were used for contraception, but did not ask about frequency or duration or diaphragm storage in talc	Areas of application of talc: –52.2% of cases and 55.1% of controls never used talc –34.0% of cases and 32.2% of controls reported talc use in the genital or thigh area – 2.8% of cases and 2.9% of controls reported talc use on sanitary napkins – 11.0% of cases and 9.8% of controls reported talc use in genital or thigh area and on sanitary napkins Duration of talc use: – 56% of cases and 58.4% of controls had no talc use – 9.1% of cases and 9.3% of controls used talc for 1-9 yr – 11.4% of cases and 7.6% of controls used talc for 10-19 yr 23.5% of cases and 24.6% of controls used talc for ≥20 yr	**OR** 1.0 1.0 (0.8-1.3) 0.9 (0.4-2.0) 1.1 (0.7-1.7) 1.0 0.9 (0.6-1.5) 1.4 (0.9-2.2) 0.9 (0.6-1.2)	173
Hospital-based cases/population-based controls						
Talc; purity and composition not specified	–215 white females in the Greater Boston area with epithelial ovarian cancer (from 12 hospitals) –215 matched pop controls	November 1978–September 1981	–Exposure to talc by way of contraceptive practices, operations, or perineal hygiene was reviewed for each patient and control –Risk was adjusted for parity and menopausal status	–42.8% of cases and 28.4% of controls had any perineal exposure as a dusting powder on the perineum or on sanitary napkins; adjusted RR was compared to patients with neither exposure –27.9% of cases and 22.3% of controls had used talc for dusting the perineum or sanitary napkins, but not both – 14.9% of cases and 6% of controls had exposure through both dusting the perineum and sanitary napkins; RR was compared to patients with neither exposure	**OR** **1.92 (1.27-2.89**; $P < 0.003$) 1.55 ($P = 0.06$) 3.28 ($P < 0.001$; (1.68-6.42)	146

(continued)

Table 9. (continued)

Talc/composition	Population/geographical area	Study/diagnosis years	Study description and limitations	Findings	OR or RR (95% CI)	Reference
Talc, purity and composition not specified; often reported as "baby powder"	–235 white women in Boston with epithelial ovarian cancer (from 10 hospitals) –239 age- and residence-matched pop controls	July 1984-September 1987	–Patients were asked questions about demographic and occupational, medical and reproductive, and dietary histories, cigarette smoking, and hygienic practices, including use of douches, type of sanitary protection, and perineal exposure to talc –Use of talc on areas other than the perineum were considered nonexposed –Risk was adjusted for parity, education, marital status, religion, use of sanitary napkins, douching, age, and wt	Ever/never perineal use of talc:	**OR**	154
				–51.5% of cases and 60.7% of controls reported no genital talc application	1.0	
				–48.5% of cases and 39.3% of controls reported perineal talc exposure	1.5 (1.0-2.1)	
				Use on sanitary napkins, underwear, and/or diaphragm:	1.1 (0.4-2.8)	
				–3.8% of cases and 5.0% of controls reported talc use on sanitary napkins and/or underwear	1.2 (0.6-2.4) **1.7 (1.1-2.7)**	
				–8.5% of cases and 8.8% of controls reported exposure with diaphragm use or from their partner in combination with sanitary napkins and/or underwear		
				–36.2% of cases and 25.5% of controls reported exposure by dusting powder to the perineum in combination with sanitary napkins and/or underwear		
				Frequency of talc application:	1.5 (0.8-2.7)	
				–13.6% of cases and 11.7% of controls reported <5 appl/mo	1.2 (0.6-2.2)	
				–10.2% of cases and 10.5% of controls reported 5-29 appl/mo	**1.8 (1.1-3.0)**	
				–24.7% of cases and 16.7% of controls reported >30 appl/mo		
				Duration of use of talc:		
				–6.0% of cases and 6.3% of controls reported <10 yr talc use	1.2 (0.5-2.6)	
				–20.9% of cases and 16.3% of controls reported 10-29 yr talc use	1.6 (1.0-2.7)	
				–21.7% of cases and 16.3% of controls reported ≥30 yr talc use	1.6 (1.0-2.7)	
				Number of lifetime applications:		
				–8.1% of cases and 7.9% of controls reported <1000 lifetime applications	1.3 (0.7-2.7)	
				–24.3% of cases and 19.2% of controls reported 1000-10 000 lifetime applications	1.5 (0.9-2.4) 1.8 (1.0-3.0)	
				16.2% of cases and 12.1% of controls reported >10 000 lifetime applications		
				Age at first use of talc:		
				–28.1% of cases and 20.9% of controls were <20 yr old	**1.7 (1.1-2.7)**	
				–11.5% of cases and 10.9% of controls were 20-25 yr old	1.2 (0.6-2.2)	
				–8.9% of cases and 7.5% of controls were >25 yr old	1.6 (0.8-3.2)	
				Years since last talc use		
				–20.4% of cases and 11.3% of controls used talc within the last 6 mo	**2.3 (1.3-4.0)**	
				–15.3% of cases and 16.3% of controls last used talc 6 mo-10 yr ago	1.1 (0.7-1.9)	
				–12.8% of cases and 11.7% of controls last used talc 10 or more yr ago	1.4 (0.8-2.6)	
			–Era of use was examined; restricted to women that were older than 10 yr in 1960 –Same adjustments listed previously were made	Era of talc use:		
				–12.3% of cases and 12.6% of controls used talc after 1960	1.1 (0.6-2.1)	
				–31.9% of cases and 23.9% of controls used talc before 1960	**1.7 (1.1-2.7)**	
			–Brand of powder used was examined; if more than 1 brand was used, the brand used most frequently and for the longest time was counted –Same adjustments listed previously were made	Brand/type of talc used:		
				–38.7% of cases and 30.1% of controls used brand or generic baby powder	**1.6 (1.1-2.5)**	
				–6.8% of cases and 7.2% of controls used deodorizing or other scented powders	1.2 (0.6-2.5)	
Talc; purity and composition not specified	–767 women from the Delaware Valley area of PA, NJ, and DE with epithelial ovarian cancer (from 39 hospitals) –1367 age- and geography-matched pop controls	1994-1998	–Patients were asked questions about sexual, menstrual, obstetric, and breast-feeding histories, history of medical condition that may be related to pelvic inflammation, OC use, tubal ligation, hysterectomy, ovarian operations, and talc exposure –Risk was adjusted for age, parity, race, familial history of ovarian cancer, OC use, tubal ligation, hysterectomy, and breast-feeding Limitations: – Low participation rate among cases and controls – Potential recall bias	Risk based on area of talc application:	**OR**	165
				–45.5% of cases and 53.3% of controls did not use talc	1.0	
				–21% of cases and 16% of controls applied talc to the genital/rectal area	**1.5 (1.1-2.0)**	
				– 10% of cases and 6.9% of controls applied talc to sanitary napkins	**1.6 (1.1-2.3)**	
				– 9% of cases and 7.3% of controls applied talc to underwear	**1.7 (1.2-2.4)**	
				– 1.3% of cases and 2.4% of controls applied talc to diaphragm/cervical cap	0.6 (0.3-1.2)	
				– 7.3% of cases and 9.2% of controls reported talc exposure via a male partner	1.0 (0.7-1.4) **1.4 (1.1-1.6)**	
				– 43.7% of cases and 37.5% of controls applied talc to feet		

(continued)

Table 9. (continued)

Talc/composition	Population/geographical area	Study/diagnosis years	Study description and limitations	Findings	OR or RR (95% CI)	Reference
				Risk based on length of application to genital/rectal area/feet: –52.3% of cases and 59.9% of controls reported no use –2.2% of cases and 1.2% of controls reported talc use of <1 yr – 10% of cases and 7.4% of controls reported talc use of 1-4 yr – 5.2% of cases and 4.3% of controls reported talc use of 5-9 yr – 30.4% of cases and 27.1% of controls reported talc use of <1 yr	1.0 2.0 (1.0-4.0) **1.6 (1.1-2.3)** 1.2 (0.8-1.9) 1.2 (1.0-1.5)	
Talc; purity and composition not specified	–170 French-Canadian women in Montreal with primary ovarian carcinomas or borderline tumors (from 2 hospitals) –111 of the cases were sporadic; 58 cases were familial – 170 age- and ethnic group-matched pop controls	1995-1996	–Patients were asked questions about reproductive factors; familial history of cancer; medical history, including use of hormone replacement therapy, use of OCs, tubal ligation, and hysterectomy; smoking, alcohol, and education; perineal talc use –Study was comparing the risk factors between familial and sporadic ovarian cancer	–10.6% of cases and 4.7% of controls reported perineal use of talc –9.91% of the sporadic cases and 12.1% of the familial cases reported perineal use of talc	$P = 0.064$ $P = 0.79$ (sporadic vs familial)	152
	–153/170 of the cases and 152/170 controls from above –101 of the cases were sporadic, 51 of the cases were familial		–Multivariate analysis was performed with 153 cases and 152 controls	–Perineal use of talc by cases vs controls –Perineal talc use by sporadic cases – Perineal talc use by familial cases	**RR** 2.49 (0.94-6.58; $P = 0.066$) 2.45 (0.85-7.07; $P = 0.098$) 3.25 (0.83-12.4; $P = 0.084$)	
Hospital-based cases/hospital- and population-based controls						
Talcum powder; purity and composition not specified	–188 women from northern California with primary epithelial cancer (from 7 hospitals) –280 matched hospital controls—259 matched pop controls	January 1983–December 1985	–The researchers stated that RR associated with talc use, tubal ligation, and hysterectomy were similar when cases were compared to both control groups; therefore the control groups were combined –Risk was adjusted for parity Limitations: – Failure to interview all eligible ovarian cancer patients and a completely random sample of controls – Cofounding by differential talc use among women with characteristics predictive of ovarian cancer (unlikely) – Random error in reported talc use	Type of talc exposure: –40% of cases and 43% of controls reported no talc use –12% of cases and 10% of controls reported talc exposure on the perineum only – 3% of cases and 5% of controls reported talc exposure on sanitary pads only – 5% of cases and 4% of controls reported talc exposure with diaphragm use only – 36% of cases and 31% of controls reported talc exposure by 2 of the 3 use types – 1% of cases and 2% of controls reported talc exposure by all 3 use types	**OR** 1.0 1.45 (0.81-2.6) 0.62 (0.21-1.80) 1.60 (0.63-3.58) 1.36 (0.91-2.04) 0.35 (0.04-2.94)	172
			–Risk was also examined based on duration of use of talcum powder; talc use after tubal ligation or hysterectomy was excluded –Risk was adjusted for parity	Duration of talc use: –55% of cases and 59% of controls did not report years of talc use –18% of cases and 13% of controls reported talc exposure of 1-9 yr – 27% of cases and 27% of controls reported talc exposure of 10+ yr – 23% of cases and 19% of controls reported 20+ talc applications/mo –overall trend for 30 uses/mo	1.0 1.60 (1.00-2.57; $P = 0.05$) 1.11 (0.82-1.96; $P = 0.61$) 1.45 (0.94-2.22) 1.30 (0.88-1.92)	

(continued)

Table 9. (continued)

Talc/composition	Population/geographical area	Study/diagnosis years	Study description and limitations	Findings	OR or RR (95% CI)	Reference
Population-based cases/population-based controls						
Talc (as baby powder) Deodorizing powders that contain other substances in addition to talc	–116 white women of western Washington state with borderline ovarian tumors (from the Seattle-Puget Sound Cancer Surveillance System) –158 white age- and residence-matched controls	1980-1985	–Patients were asked questions about reproductive and sexual history, medical history, and perineal exposure to talc –Risk was adjusted for age, parity, and use of oral contraceptives Limitations: – Only 30% of potentially eligible cases and controls participated	Types of exposure to talc: –57.8% of cases and 59.5% of controls reported no perineal exposure to powder – 42.2% of cases and 40.5% of controls reported any perineal exposure to powder – 6.9% of cases and 13.3% of controls reported powder exposure by diaphragm storage only – 9.5% of cases and 17.1% of controls reported powder exposure by diaphragm storage or by other methods – 20.7% of cases and 19.0% of controls reported powder exposure following bathing only – 29.3% of cases and 23.4% of controls reported powder exposure following bathing or by other methods – 6.0% of cases and 2.5% of controls reported powder exposure by use on sanitary napkins only – 12.1% of cases and 6.3% of controls reported powder exposure by use on sanitary napkins or by other methods – 6.0% of cases and 23.4% of controls reported after bathing and on sanitary napkins Type of powder used (ie, baby, deodorizing, or cornstarch) –15.5% of cases and 19.6% of controls reported baby powder only – 19.0% of cases and 21.5% of controls reported baby powder only or combined use – 11.2% of cases and 12.0% of controls reported talc, unspecified (no combined use) – 3.4% of cases and 4.4% of controls reported cornstarch only – 8.6% of cases and 2.5% of controls reported deodorizing powder only – 12.1% of cases and 4.4% of controls reported deodorizing powder only or combined use Route of talc exposure and type of powder used: –Any powder use after bathing –8.6% of cases and 3.8% of controls reported any use of deodorizing powder –20.7% of cases and 20.3% of controls reported no use of deodorizing powder – Any powder use on sanitary napkins – 6.9% of cases and 2.5% of controls reported any use of deodorizing powder –5.2% of cases and 3.8% of controls reported no use of deodorizing powder	**RR** 1 1.1 (0.7-2.1) 0.5 (0.2-1.4) 0.5 (0.2-1.3) 1.2 (0.6-2.6) 1.3 (0.8-2.7) 2.2 (0.8-19.8) 1.9 (0.9-6.9) 2.2 (0.8-18.8) 0.8 (0.4-1.9) 0.9 (0.5-2.0) 1.0 (0.4-2.4) 0.8 (0.2-3.8) **3.5 (1.2-28.7)** **2.8 (1.1-11.7)** 3.1 (0.8-10.9) 1.1 (0.5-2.4) 2.6 (0.9-22.4) 1.5 (0.4-6.5)	153
Talc-containing dusting powder; purity and composition not specified	–112 females in Beijing, China with epithelial ovarian cancer (from Beijing Cancer Registry) –224 age-matched community controls	1984-1986	–Patients were asked questions about menstrual, obstetric, marital, medical, and familial histories –Risk was adjusted for education and parity –Risk with occupational exposure was also determined Limitations: Some ovarian cancer patients may not have been ascertained for the study – High rate of loss due to deaths could reflect on survival and on risk – Exclusion of controls with current health problems	Types of talc exposure: –93.8% of cases and 97.8% of controls reported no use of dusting powder –6.3% of cases and 2.2% of controls reported dusting powder use on the lower abdomen and perineum – Number of cases and controls exposed occupationally to talc (occupation was not specified)	**RR** 1.0 3.9 (0.9-10.6) 0.9 (0.3-2.9)	144

(continued)

Table 9. (continued)

Talc/composition	Population/geographical area	Study/diagnosis years	Study description and limitations	Findings	OR or RR (95% CI)	Reference
5 categories of powder: talcum, cornstarch, baby, deodorant, and scented body/ bath	–313 white women in western WA (pop based) with epithelial ovarian cancer –422 white age- and geography-matched pop controls	January 1986–December 1988	–Patients were questioned about genital powder exposure, demographic characteristics, reproductive, medical, and smoking histories, and birth control methods –Risk was adjusted for age; further adjustment for education, income, marital status, BMI, OC use, or parity did not alter the estimated RRs Limitations: – A sizeable number of eligible women, particularly those with ovarian cancer, did not participate – Difficult to ascertain whether perineal powder application correctly estimates actual exposure to particles – Direct comparison with other studies is limited because of differences in definitions, groupings, and analysis of genital powder use – Insufficient information to address influence of condom use on risk	Ever/never genital use of talc: –49.2% of cases and 60.7% of controls reported no lifetime genital powder application –50.8% of cases and 39.3% of controls reported any lifetime genital powder application	**OR** 1.0 **1.5 (1.1-2.0)**	145
				Exclusive use of powder: –17.6% of cases and 11.4% of controls reported perineal dusting only –7.0% of cases and 8.3% of controls reported diaphragm storage in powder only – 3.8% of cases and 2.4% of controls reported powder on sanitary napkins only 5.8% of cases and 6.6% of controls reported genital deodorant spray only	**1.8 (1.2-2.9)** 0.8 (0.4-1.4) 1.5 (0.6-3.6) 1.5 (0.8-3.0)	
			–Risk was adjusted for age and other methods of genital powder application	Any perineal dusting and CLE (days): –30.4% of cases and 20.6% of controls reported any dusting –6.4% of cases and 5.2% of controls reported ≤2000 days CLE – 7.7% of cases and 6.2% of controls reported 2001-5000 CLE – 6.7% of cases and 5.2% of controls reported 5001-10 000 CLE – 8.9% of cases and 4.0% of controls reported >10 000 CLE	1.8 (0.9-3.5) 1.6 (0.9-2.9) 1.2 (0.6-2.4) 1.8 (0.9-3.4)	
			–Risk was adjusted for age and other methods of genital powder application	Any diaphragm storage in powder CLE (mo): –14.7% of cases and 12.1% of controls reported diaphragm storage in powder –7.7% of cases and 6.2% of controls reported ≤60 mo CLE – 4.8% of cases and 4.7% of controls reported >60 mo CLE	1.0 (0.6-1.6) 1.1 (0.6-1.9) 0.8 (0.4-1.7)	
			–Risk was adjusted for age and other methods of genital powder application (none/any)	Any powder on sanitary napkins and CLE (mo) and applications: –12.1% of cases and 9.5% of controls reported any powder on sanitary napkins –8.0% of cases and 5.0% of controls reported ≤120 mo CLE – 3.8% of cases and 4.5% of controls reported >120 mo CLE – 7.3% of cases and 4.5% of controls reported ≤1000 lifetime applications – 4.5% of cases and 5.0% of controls reported >1000 lifetime applications	0.9 (0.5-1.5) 1.3 (0.7-2.4) 0.5 (0.2-1.1) 1.3 (0.7-2.5) 0.6 (0.3-1.2)	
			–Risk was adjusted for age and other methods of genital powder application	Any genital deodorant spray and CLE (mo) and applications: –12.8% of cases and 9.5% of controls reported any genital deodorant spray –7.7% of cases and 7.4% of controls reported ≤12 mo CLE – 4.8% of cases and 2.1% of controls reported >12 mo CLE – 9.3% of cases and 8.1% of controls reported ≤500 lifetime applications – 3.2% of cases and 1.4% of controls reported >500 lifetime applications	**1.9 (1.1-3.1)** 1.5 (0.9-2.8) **2.7 (1.1-6.6**; $P<0.05$) 1.7 (1.0-2.9) 2.6 (0.9-7.6; $P<0.05$)	
			–Risk was adjusted for age	Exclusive use by powder type: –5.1% of cases and 3.8% of controls used talcum powder only –9.9% of cases and 8.5% of controls used baby powder only – 1.6% of cases and 2.6% of controls used cornstarch only – 2.9% of cases and 2.4% of controls used deodorizing powder only – 8.6% of cases and 5.9% of controls used bath/body powder only	1.2 (0.6-2.5) 1.4 (0.8-2.4) 0.9 (0.3-2.9) 1.0 (0.4-2.6) 1.6 (0.9-3.0)	

(continued)

Table 9. (continued)

Talc/composition	Population/geographical area	Study/diagnosis years	Study description and limitations	Findings	OR or RR (95% CI)	Reference
			–Risk was adjusted for age and use of other types of powders (yes/no)	Use of any powder type:		
				–10.5% of cases and 5.5% of controls reported any talcum powder	1.6 (0.9-2.8)	
				–16.6% of cases and 14.5% of controls reported any baby powder	1.1 (0.7-1.8)	
				–2.6% of cases and 3.8% of controls reported any cornstarch	0.8 (0.3-2.0)	
				–7.7% of cases and 5.7% of controls reported any deodorizing powder	1.1 (0.6-2.0)	
				–16.6% of cases and 10.2% of controls reported any bath/body powder	1.5 (0.9-2.4)	
			–The tumors were stratified by histological subtype –Risk was adjusted for age	Controls (422 total):	**RR**	
				–60.7% never used powder perineally	1.0	
				–39.3% ever used powder perineally	**1.7 (1.1-2.5)**	
				All serous tumors (131 total):	0.7 (0.4-1.4)	
				–45.8% never used powder perineally	1.2 (0.6-2.3)	
				– 54.2% ever used powder perineally	**1.8 (1.1-2.8)**	
				Serous tumors (43 total) 67.4% never used use powder perineally – 32.6% ever used powder perineally Endometroid tumors (36 total): – 52.8% never used use powder perineally – 47.2% ever used powder perineally Other tumors (103 total); (17 clear cell; 3 undifferentiated; 83 unclassified adenocarcinomas or unspecified carcinomas): – 44.7% never used powder perineally – 55.3% ever used powder perineally		
Talc; purity and composition not specified	–189 women in Greater Athens with epithelial ovarian tumors (2 hospitals) –200 hospital visitor controls	June 1989-March 1991	–The women were asked about smoking; alcohol and coffee consumption; reproductive history; frequency of use of analgesics, tranquilizers, or hypnotics; talc in the perineal region; hair dyes –Multiple regression adjusted for age, years of schooling, body wt prior to onset, age at menarche, parity, menopausal status, age at first birth and at menopause, smoking, coffee drinking, alcohol consumption, hair dyeing, talc application, use of analgesics, and tranquilizers/hypnotics, and for mutual confounders Limitations: – Moderate study size – Possibility of selection bias – Possibility of information bias	–3.1% of cases and 3.5% of controls reported talc application in the perineum – A crude RR, age-adjusted RR, and multiple regression RR were determined	**OR** 0.90 (crude; 0.30-2.74) 0.86 (age-adjusted; 0.27-2.68) 1.05 (multiple regression; 0.28-3.98)	170
Talc, purity and composition not specified, and cornstarch	–450 women from Toronto and Ontario, Canada with epithelial ovarian cancer (pop based) –564 age-matched pop-based controls	November 1989-October 1992	–Patients were questioned about medical and reproductive histories, menstrual characteristics, pregnancies, hormone and contraceptive use, and talc (and cornstarch) usage, type, and exposure –Risk was adjusted for age, OC use, parity, breastfeeding, tubal ligation, hysterectomy, and family history of ovarian or breast cancer –Risk was adjusted as above	Powder-type exposures:	**OR**	143
				44% of cases and 35.6% of controls reported any talc exposure	**1.42 (1.08-1.86)**	
				–0.44% of cases and 0.85% of controls reported any cornstarch exposure	0.31 (0.06-1.66)	
				– 0.89% of cases and 1.24% of controls reported cornstarch/talc exposure	0.68 (0.18-2.33)	
				– 11.3% of cases and 8.7% of controls reported talc exposure via sanitary napkins	1.26 (0.81-1.96)	
				–38.2% of cases and 10.5% of controls reported talc exposure after bathing	1.31 (1.0-1.73)	
				Frequency (per mo) of after-bath talc use:		
				–Mean uses/mo after-bath talc was 14.6 for cases and 17.2 for controls	0.89 (0.74-1.07)	
				–16.9% of cases and 10.5% of controls reported <10 uses/mo after-bath talc	**1.84 (1.24-2.73)**	
				– 12.8% of cases and 11.3% of controls reported 10-25 uses/mo after-bath talc	1.13 (0.74-1.72)	
				– 9.1% of cases and 10.6% of controls reported >25 uses/mo after-bath talc	0.95 (0.61-1.49)	

(continued)

Table 9. (continued)

Talc/composition	Population/geographical area	Study/diagnosis years	Study description and limitations	Findings	OR or RR (95% CI)	Reference
			–It was assumed the regular after-bath talc use commenced at age 20 –Risk was adjusted as above	Duration of after-bath talc use: –Mean years after-bath talc use was 32.9 yr for cases and 35.4 yr for controls –13.3% of cases and 9.2% of controls reported <30 yr after-bath talc use – 15.8% of cases and 11.9% of controls reported 30-40 yr after-bath talc use – 9.1% of cases and 11.3% of controls reported >40 yr after-bath talc use	1.09 (0.98-1.21) **1.7 (1.09-2.64)** 1.44 (0.96-2.15) 0.87 (0.54-1.38)	
			–Risk was adjusted as above	After-bath talc use pre/post 1970: –Case mean was 26.4 yr and control mean was 24.9 yr after-bath talc use before 1970 –Case mean was 6.5 yr and control mean was 10.4 yr after-bath talc use after 1970	1.09 (0.98-1.22) 1.1 (0.89-1.35)	
Talc; purity and composition not specified	–200 women in Israel with primary invasive (164) or borderline (36) epithelial ovarian cancer (Israel Cancer Registry) –408 geography-matched pop controls	January 1990-September 1993	–Patients were asked questions about obstetric and gynecologic history, including infertility and treatment, smoking, education, and talc usage Limitations: –No access to medical records to verify information – Possibility of recall bias – Possibility that results were confounded by a specific cause of infertility	–89.0% of cases and 94.4% of controls reported never-seldom use of talc –10.5% of cases and 5.6% of controls reported moderate—a lot use of talc ($P = 0.04$)	Not given	169
Talc; purity and composition not specified	–824 women in Queensland, New South Wales, and Victoria, Australia with epithelial ovarian cancer (gynecological–oncology registries) –860 age- and geography-matched pop controls	August 1990-December 1993	–Patients were asked questions about education and ethnicity, and obstetric, marital, occupational, medical, and familial histories, childhood mumps history, and use of talc –Risk was adjusted for parity Limitations: – Potential selection bias	–56.7% of cases and 52.0% of controls used talc around the abdomen/perineum	**OR** **1.27 (1.04-1.54)**	166
Talc, baby powder, deodorizing powders; purity and composition not specified	–563 women in eastern MA and NH with epithelial ovarian cancer (pop based) –523 age-matched pop controls – (Phase I of the New England Case Control [NECC] study)	May 1992-March 1997	–Patients were asked questions about demographics, reproductive and menstrual history, medical history, personal habits, and whether talc, baby, or deodorizing powders were dusted or sprayed regularly and age at first use, type of powder, applications/months, and total years of use –Risk was adjusted for age, study center, tubal ligation, BMI, parity, OC use, and family history of breast/ovarian cancer Limitations: –Possible recall bias – Potential bias from confounding –Risk adjusted as above	Exposure to talc: –55.4% of cases and 63.9% of controls reported no personal use of talc –17.6% of cases and 18.0% of controls reported use of talc in nongenital areas – 12.6% of cases and 9.8% of controls reported exposure through dusting of the perineum – 3.6% of cases and 2.3% of controls reported exposure through dusting sanitary napkins – 1.4% of cases and 1.2% of controls reported exposure through dusting underwear – 9.4% of cases and 5.0% of controls reported multiple uses in the genital area	**OR** 1.0 1.08 (0.77–1.50) 1.45 (0.97-2.18) 1.45 (0.68-3.09) 1.21 (0.40-3.64) **2.15 (1.30-3.57)**	148
				Ever/never genital talc use: –73% of cases and 81.8% of controls reported no genital talc use –27.0% of cases and 18.2% of controls reported any genital use	1.0 **1.60 (1.18-2.15)**	
			–Risk was adjusted for age, study center, tubal ligation, and use of other powders	Type of powder used: –26.4% of cases and 17.6% of controls reported use of talc –0.2% of cases and 0.6% of controls reported use of cornstarch	**1.69 (1.26-2.27)** 0.31 (0.03-3.01)	
			Patients with no personal use were asked about use by husband –Risk was adjusted as above	No personal use/use of talc by husband: –87.6% of cases and 92% of controls reported no husband talc use –12.4% of cases and 8.0% of controls reported husbands did use talc	1.0 1.52 (0.92-2.52)	
			–Risk was adjusted for age, study center, tubal ligation, BMI, parity, OC use, and family history of breast/ovarian cancer	Frequency of use per month for total of all uses in the genital area: –11.5% of cases and 5.4% of controls reported <30 uses/mo –10.6% of cases and 9.8% of controls reported 30-39 uses/mo – 9.8% of cases and 2.9% of controls reported 40+ uses/mo	**2.21 (1.37-3.56)** 1.17 (0.78-1.76) 1.57 (0.80-3.10)	

(continued)

Table 9. (continued)

Talc/composition	Population/geographical area	Study/diagnosis years	Study description and limitations	Findings	OR or RR (95% CI)	Reference
			–Risk was adjusted as above	Duration of talc use:		
				–9.9% of cases and 5.9% of controls reported <20 yr talc use	**1.86 (1.16-3.00)**	
				–5.8% of cases and 5.0% of controls reported 20-30 yr talc use	1.33 (0.76-2.30)	
				–10.6% of cases and 7.1% of controls reported ≥30 yr talc use	1.44 (0.91-2.26)	
				– *P* value for linear trend, excluding nongenital exposure	*P* = 0.477	
				– *P* value for linear trend, including nongenital exposure	*P* = 0.062	
			–Same adjustments listed previously were made	Total applications:		
				9.2% of cases and 5.2% of controls applied talc <3000×	**1.84 (1.12-3.30)**	
				–6.5% of cases and 5.4% of controls applied talc 3000-10 000×	1.43 (0.84-2.41)	
				– 6.5% of cases and 3.8% of controls applied talc >10 000×	1.43 (0.92-2.22)	
				– *P* value for linear trend, excluding nongenital exposure	0.164	
				– *P* value for linear trend, including nongenital exposure	0.472	
			–Same adjustments listed previously were made	Age at first use of talc:		
				–17.4% of cases and 12.8% of controls were <20 yr old	**1.46 (1.03-2.07)**	
				–6.5% of cases and 3.4% of controls were 20-25 yr old	**1.87 (1.03-3.39)**	
				–2.3% of cases and 1.7% of controls were >25 yr old	1.54 (0.64-3.72)	
				– *P* value for linear trend including nonexposed patients	*P* = 0.504	
			–The tumors were stratified by histological subtype		**OR**	
			–Risk was adjusted for age, BMI, primary relevance with breast or ovarian cancer, parity, OC use, tubal ligation, and study center	Controls (523 total):	1.0	
				–81.8% never used talc perineally	1.38 (0.82-2.31)	
				18.2% ever used talc perineally	**1.70 (1.22-2.39)**	
				Serous borderline tumors (86 total):	0.79 (0.44-1.40)	
				– 73.3% never used talc perineally	1.04 (0.67-1.61)	
				– 26.7% ever used talc perineally	1.44 (0.67-3.08)	
				Serous invasive tumors (229 total):		
				– 68.6% never used use talc perineally		
				– 31.4% ever used talc perineally		
				Mucinous tumors (83 total):		
				– 80.7% never used talc perineally		
				– 19.3% ever used talc perineally		
				Endometroid/clear cell tumors (130 total):		
				– 76.2% never used use talc perineally		
				– 23.8% ever used talc perineally		
				Undifferentiated tumors (35 total):		
				– 71.4% never used use talc perineally		
				– 28.6% ever used talc perineally		
Talc; purity and composition not specified	–668 women in eastern MA and NH with invasive ovarian cancer (pop based) –721 age-matched pop controls – (Phase 2 of the NECC)	July 1998-July 2003	–Risk for ovarian cancer with talc use was determined –Risk was adjusted for age, study center, parity, nonwhite race, and Jewish religion Limitations: –Exposure information was collected by self-report, introducing the possibility of misclassification – Inability to directly compare anti-MUC1 antibody levels in cases and controls to calculate an OR	Talc use: –47.8% of cases and 47.6% of controls reported no talc use –32.0% of cases and 28.2% of controls reported genital use of talc – 20.2% of cases and 24.1% of controls reported body use of talc only	**OR** 1.0 1.16 (0.90-1.49; P=0.25) 0.87 (0.65-1.15; P=0.33)	149

(continued)

Table 9. (continued)

Talc/composition	Population/geographical area	Study/diagnosis years	Study description and limitations	Findings	OR or RR (95% CI)	Reference
Talc; purity and composition not specified	–210 women with ovarian cancer –600 birth-, DNA type-, and menopausal status-matched controls (these are patients included in the Nurses' Health Study that provided blood or buccal samples)	1989-2004	–Examined whether an association between genital talc exposure and ovarian cancer risk is modified by variants of the *NAT2* and *GSTM1* genes and the *GSTT1* gene –Patients were asked about application of talcum, baby or deodorizing powder to the perineal area or sanitary napkins – Risk with regular talc use and frequency of genital talc use was determined –Risk was adjusted for the matching factors, duration of oral contraceptive use, parity, tubal ligation, BMI, and duration of PMH use Limitations: – Inability to detect interactions with certain combinations of genes and for specific histologic subtypes – Loss of some detail due to the use of common exposure and covariate definitions (particularly for the NECC)	Total epithelial cancer (210 cases; 600 controls): –40% of cases and 39% of controls reported any history of genital talc use –70.8% of cases and 76% of controls reported no regular genital talc use (1×/wk or more) – 29.2% of cases and 24% of controls reported regular genital talc use Frequency of genital talc use: – 61.5% of cases and 64.6% of controls reported no frequency of genital talc use – 9.2% of cases and 11.4% of control reported use <1×/wk – 11.3% of cases and 11.2% of controls reported use 1-6×/wk – 18% of cases and 13% of controls reported daily genital talc use – P_{trend} for frequency of genital talc use	**OR** $P = 0.79$ 1.0 1.24 (0.83-1.83; $P = 0.15$) 1.0 0.98 (0.54-1.79) 1.01 (0.57-1.79) 1.44 (0.88-2.37; $P = 0.08$) 0.18	150
				Serous invasive ovarian cancer (93 cases; 263 controls) –68.2% of cases and 73.8% of controls reported no regular genital talc use – 31.8% of cases and 26.3% of controls reported regular genital talc use Frequency of genital talc use: – 61.4% of cases and 62.9% of controls reported no frequency of genital talc use – 6.8% of cases and 10.8% of control reported use <1×/wk – 13.6% of cases and 10.4% of controls reported use 1-6×/wk – 18.2% of cases and 15.8% of controls reported daily use – P_{trend} for frequency of genital talc use	1.0 1.48 (0.82-2.68) 1.0 0.79 (0.29-2.11) 1.64 (0.71-3.79) 1.34(0.65-2.76) 0.29	
	–1175 women from MA and NH with epithelial ovarian cancer –1202 age- and state-matched pop controls – (Pooled data from patients in phase 1 and phase 2 of the NECC that provided a blood specimen)	May 1992-July 2003	–Patients were asked about use of talcum, baby or deodorizing powder, type of use of the powder, frequency of use, number of years of use, brand used –Risk was adjusted for the matching factors, duration of OC use, parity, tubal ligation, BMI, and duration of PMH use –Risk with regular talc use and frequency of genital talc use was determined – Risk was adjusted for age, study center, duration of OC use, parity, tubal ligation, BMI, and duration of PMH use	Total epithelial cancer (1175 cases; 1202 controls): –29% of cases and 24% of controls reported any history of genital talc use –73.2% of cases and 79.7% of controls reported no regular genital talc use (1×/wk or more) – 26.8% of cases and 20.3% of controls reported regular genital talc use Frequency of genital talc use: – 70.9% of cases and 76.3% of controls reported no frequency of genital talc use – 2.3% of cases and 3.4% of control reported use <1×/wk – 10.5% of cases and 8.0% of controls reported use 1-6×/wk – 16.3% of cases and 12.3% of controls reported daily genital talc use – P_{trend} for frequency of genital talc use	**$P = 0.003$** 1.0 **1.40 (1.15-1.70; $P < 0.001$)** 1.0 0.72 (0.43-1.19) 1.33 (1.00-1.79) **1.41 (1.10-1.79; $P = 0.006$)** **0.002**	
				Serous invasive ovarian cancer (450 cases; 1202 controls): –69.0% of cases and 79.7% of controls reported no regular genital talc use –31.0% of cases and 20.3% of controls reported genital talc use – 66.6% of cases and 76.3% of controls reported no frequency of genital talc use 2.4% of cases and 3.4% of control reported use <1×/wk – 12.5% of cases and 8.0% of controls reported use 1-6×/wk – 18.5% of cases and 12.3% of controls reported daily use – P_{trend} for frequency of genital talc use	1.0 **1.62 (1.26-2.09)** 1.0 0.65 (0.32-1.33) **1.56 (1.08-2.26)** **1.61 (1.18-2.20)** **<0.001**	

(continued)

Table 9. (continued)

Talc/composition	Population/geographical area	Study/diagnosis years	Study description and limitations	Findings	OR or RR (95% CI)	Reference
	–Pooled analysis of the NECC study (phase I and phase 2 combined) and the 210 cases and 600 controls from the Nurses' Health Study (presented above)		–The researchers analyzed the interactions between talc use and genes in detoxification pathways	Total epithelial cancer: –No regular genital talc use (1×/wk or more) –Any reported regular genital talc use Frequency of genital talc use – No frequency of genital talc use – Reported use <1×/wk – Reported use 1-6×/wk – Reported daily genital talc use – P_{trend} for frequency of genital talc use Serous invasive ovarian cancer: –Reported no regular genital talc use Reported any genital talc use – No frequency of genital talc use – 2 reported use <1×/wk – Reported use 1-6×/wk – Reported daily use – P_{trend} for frequency of genital talc use – There was no clear evidence of an interaction with *GSTM1* alone or *NAT2*	 1.0 1.36 (1.13-1.63) 1.0 0.82 (0.55-1.20) 1.26 (0.97-1.63) **1.41 (1.14-1.76)** **<0.001** 1.0 **1.60 (1.26-2.02)** 1.0 0.70 (0.39-1.24) **1.12-2.21)** **1.56 (1.17-2.08)** **<0.001**	
Talc; purity and composition not specified	"Average risk" women from the 3 phases without hysterectomy or family history of cancer: –1098 women with invasive ovarian cancer (pop based) –1363 age-matched pop controls that were >40 yr old (includes women from NECC phases I and 2, and the 897 phase 3 cases and 857 phase3 controls)	1992-2008 (all 3 phases) (phase 3: 2003-2008)	–Phase 1[148] and phase 2[149] described previously –Reviewed relative risk for "average risk" women (excluded women at high risk of breast or ovarian cancer) Limitations: Use of case control data to develop the scoring system because of: – Potential for recall bias – Potential for selection bias – The calculation of only RR and not absolute risk	Long-term use of talc: –84.9% of cases and 88.8% of controls reported no long-term (10+ yr) talc use –15.1% of cases and 11.2% of controls reported long-term talc use	**OR** 1.0 **1.42 (1.12-1.81;** $P = 0.004$)	171
Talc; purity and composition not specified	–609 women from Los Angeles county with ovarian cancer (pop based) –688 race/ethnicity- and age-matched controls	1998-2002	–Patients were asked questions about medical, gynecological, reproductive, and lifestyle histories, family history of breast or ovarian cancer, OC use; tubal ligation or hysterectomy; use of NSAIDs, and talc use –risk was adjusted for race, age, education, tubal ligation, cancer history, menopausal status, OC use, parity	Use of talc –60% of cases and 68.2% of controls never used talc – 40% of cases and 31.8% of controls ever used talc – 18.5% of case and 15% of control talc users used talc in nonperineal area – 21.5% of case and 16.9% of control talc users used talc in perineal area Frequency and duration of talc use –5.8% of cases and 4.5% of controls used talc for ≤20 yr and ≤10×/mo – 3.8% of cases and 4.4% of controls used talc for ≤20 yr and >10—≤30×/mo – 3.5% of cases and 3.1% of controls used talc for ≤20 yr and ≥30×/mo – 7.4% of cases and 7.1% of controls used talc for >20 yr and ≤10×/mo – 8.4% of cases and 6.3% of controls used talc for >20 yr and >10—≤30× /mo – 11.1% of cases and 6.5% of controls used talc for ≥20 yr and ≥30×/mo Total number of talc uses –8.1% of cases and 7.6% of controls used talc ≤5200× – 7.6% of cases and 6.8% of controls used talc >5200-≤15 600× – 10.4% of cases and 8.9% of controls used talc >15 600-≤52 000× – 13.9% of cases and 8.6% of controls used talc >52 000×	**RR** 1.0 **1.48 (1.15-1.91)** **1.43 (1.03-1.98)** **1.53 (1.13-2.09)** 1.36 (0.79-2.32) 1.16 (0.63-2.12) 1.23 (0.63-2.41) 1.27 (0.80-2.01) 1.57 (0.99-2.50) **2.08 (1.34-3.23)** 1.2 (0.77-1.88) 1.38 (0.87-2.20) 1.34 (0.89-2.02) **1.99 (1.34-2.96)**	174

(continued)

Table 9. (continued)

Talc/composition	Population/geographical area	Study/diagnosis years	Study description and limitations	Findings	OR or RR (95% CI)	Reference
			–Examined risk based on total number of talc uses before/after 1975	Before 1975:		
				–4.0% of cases and 5.1% of controls used talc ≤5200×	0.84 (0.47-1.51)	
				–4.8% of cases and 4.2% of controls used talc >5200-≤15 600×	1.41 (0.79-2.53)	
				– 8.1% of cases and 6.5% of controls used talc >15 600-≤52 000×	1.45 (0.91-2.31)	
				– 13.6% of cases and 8.4% of controls used talc >52 000×	**1.93 (1.29-2.88)**	
				After 1975:	1.95 (0.98-3.89)	
				– 4.1% of cases and 2.5% of controls used talc ≤5200×	1.17 (0.56-2.48)	
				– 2.8% of cases and 2.6% of controls used talc >5200-≤15 600×	0.98 (0.45-2.13)	
				– 2.6% of cases and 2.5% of controls used talc >15 600		
Talc; purity and composition not specified	–83 African-American and 550 white women from 48 counties of NC with epithelial ovarian cancer –134 African-American and 533 white age-, race/ ethnicity-, and geographical region-matched controls	1999-2008	–Examined risk factors in African-American vs white women, including use of talc –Risk was adjusted for age Limitations: –Relatively small sample size of African-American women – Modest sample size precluded conducting analyses within subgroups – Participation bias	African-American women:	**OR**	163
				–54.2% of cases and 56.0% of controls reported no talc use	1.0	
				–45.8% of cases and 44.0% of controls reported any talc use	1.19 (0.68-2.09)	
				White women:	1.0	
				– 59.6% of cases and 61.0% of controls reported no talc use	1.04 (0.82-1.33)	
				– 40.4% of cases and 39.0% of controls reported any talc use		
Talc; purity and composition not specified	–256 women from 22 central CA counties with epithelial ovarian cancer (pop based) –1122 age- and ethnicity-matched controls	2000-2001	— Patients were asked questions on menstrual, reproductive, gynecological, surgical, and family cancer histories, use of exogenous hormones –Examined risk with talc use based on frequency, duration, and cumulative use and timing of use – Numbers were adjusted based on available data – Risk was adjusted for age, race/ethnicity, OC use, and breastfeeding Limitations: – Relatively small sample size – Low response fraction – Possible recall bias – Inability to exclude use during nonovulatory periods or and posttubal ligation or hysterectomy – Inability to differentiate among formulations used	Ever/never use of talc:	**OR**	162
				–57.4% of cases and 62.9% of controls never used talc	1.0	
				–42.6% of cases and 37.1% of controls ever used talc	**1.37 (1.02-1.85)**	
				Frequency of use:	1.34 (0.87-2.08)	
				– 13.4% of cases and 12.5% of controls used talc rarely to several times/mo	1.16 (0.74-1.81)	
				– 12.4% of cases and 13.2% of controls used talc 1-3×/wk	**1.74 (1.14-2.64)**	
				– 16.5% of cases and 11.1% of controls used talc 4-7×/wk	**0.015**	
				– P_{trend}		
				Duration of use		
				–7.4% of cases and 9.2% of controls used talc for ≤3 yr	1.01 (0.58-1.76)	
				– 13.2% of cases and 9.1% of controls used talc for 4-12 yr	**1.86 (1.16-2.98)**	
				– 11.9% of cases and 9.4% of controls used talc for 13-30 yr	1.45 (0.90-2.32)	
				– 8.6% of cases and 8.1% of controls used talc for >30 yr	1.22 (0.72-2.08)	
				– P_{trend}	**0.045**	
				Cumulative use (frequency × duration):		
				–7.4% of cases and 8.8% of controls were in the first quartile (lowest	1.03 (0.59-1.80)	
				exposure)	**1.81 (1.10-2.97)**	
				–11.5% of cases and 8.8% of controls were in second quartile	**1.74 (1.11-2.73)**	
				– 14.0% of cases and 9.9% of controls were in third quartile	1.06 (0.62-1.83)	
				– 8.2% of cases and 8.1% of controls were in fourth quartile (highest	0.051	
				exposure)		
				– P_{trend}		
				Year of first use:		
				–21.5% of cases and 19.4% of controls before/during 1975	1.22 (0.84-1.77)	
				–19.4% of cases and 15.0% of controls after 1975	**1.92 (1.27-2.91)**	
				Age at first use:		
				–12.4% of cases and 16.0% of controls were <20 yr old	0.95 (0.61-1.48)	
				–10.7% of cases and 5.8% of controls were 20-24 yr old	**2.41 (1.43-4.09)**	
				– 17.8% of cases and 12.6% of controls were ≥25 yr old	**1.80 (1.19-2.73)**	
				First use before or after first birth:		
				–18.8% of cases and 23.8% of controls prior to first birth	0.98 (0.64-1.48)	
				–22.0% of cases and 10.6% of controls after first birth	**2.51 (1.63-3.87)**	

(continued)

Table 9. (continued)

Talc/composition	Population/geographical area	Study/diagnosis years	Study description and limitations	Findings	OR or RR (95% CI)	Reference
				Years since last use:		
				–13.2% of cases and 12.5% of controls are current users	1.27 (0.81-1.98)	
				–11.2% of cases and 5.8% of controls used talc 1-2 yr ago	**2.40 (1.43-4.05)**	
				– 8.3% of cases and 7.8% of controls used talc 3-20 yr ago	1.57 (0.90-2.73)	
				– 8.3% of cases and 8.3% of controls used talc >20 yr ago	1.13 (0.66-1.94)	
Talc; purity and composition not specified	–1576 women from Australia with epithelial ovarian cancer –1509 age- and state-of-residence-matched pop controls	January 2002-September 2005	–Patients were asked questions about medical and surgical and family cancer histories, lifestyle habits, reproductive factors, hysterectomy/tubal ligation, and talc use –Risk was adjusted for age, education, parity, and OC use Limitations: – Low response rate for controls, which could result in selection bias – Medical histories were self-reported	–54% of cases and 57% of controls reported never using talc in the perineal region	**OR** 1.0	161
				– 46% of cases and 43% of controls reported ever using talc in the perineal region	**1.17 (1.01-1.36)**	
				Duration of use (with no ligation/hysterectomy)	1.13 (0.90-1.41)	
				– 13% of cases and 13% of controls reported 0-10 yr talc use	1.08 (0.87-1.34)	
				– 14% of cases and 15% of controls reported >10-25 yr talc use	**1.29 (1.04-1.58)**	
				– 19% of cases and 16% of controls reported >25 yr talc use – P_{trend}	**0.021**	
Talc; purity and composition not specified	–230 women with serous ovarian tumors and 133 women with benign mucinous tumors in Australia –752 pop controls	2002-2005	–Examined the association between use of talc and the risk of benign mucinous and serous ovarian tumors –Risk was adjusted for age, state of residence, education, parity, hormonal contraceptive use, hysterectomy, and smoking status – OR for each factor examined is presented in the order mucinous, serous, combined	–56% of mucinous cases, 55% of serous cases, and 56% of controls reported no talc use in the perineal region	**OR** 1.0	157
				– 44% of mucinous cases, 45% of serous cases, and 44% of controls reported talc use in the perineal region	1.19 (0.80-1.76) 1.04 (0.75-1.43) 1.10 (0.84-1.45)	
				Amount of talc used in the perineal region:		
				– 11% of mucinous cases, 6% of serous cases, and 10% of controls reported minimal talc use in the perineal region	1.02 (0.53-1.98) 0.70 (0.37-1.30) 0.85 (0.52-1.38)	
				–14% of mucinous cases, 9% of serous cases, and 11% of controls reported moderate talc use in the perineal region	1.57 (0.87-2.84) 0.85 (0.49-1.48) 1.05 (0.68-1.64)	
				–18% of mucinous cases, 27% of serous cases, and 21% of controls reported substantial talc use in the perineal region	0.98 (0.58-1.66) 1.21 (0.82-1.79) 1.16 (0.83-1.62)	
				P_{trend} for:		
				mucinous tumors	0.9	
				serous tumors	0.2	
				combined	0.3	
Dusting powder, many contain talc	–812 women from 13 counties in western WA state with epithelial ovarian cancer (pop-based) –1313 age-matched pop controls	January 2002-December 2005	–Patients were asked questions about lifestyle, medical, reproductive, and contraceptive histories, use of contraceptive and menopausal hormone preparations, and genital powder exposure –Risk was adjusted for age, year of diagnosis, residence, parity, and hormonal contraception – Patients were asked to report the types of powders used after bathing, including talcum, baby, cornstarch, deodorant, body/bath, and other or unknown	– 86.2% of cases and 88.5% of control reported never using powder after bathing	**OR** 1.0	168
				– 13.8% of cases and 11.5% of controls reported use of powder after bathing	1.27 (0.97-1.66)	
				– 93.2% of cases and 91.7% of controls did not use powder on sanitary napkins	1.0	
				– 6.8% of cases and 8.3% of controls used powder on sanitary napkins	0.82 (0.58-1.16)	
				– 77.7% of cases and 72.6% of controls (that were diaphragm users) did not use powder on diaphragms	1.0	
				– 22.3% of cases and 27.4% of controls (that were diaphragm users) used powder on diaphragms	0.72 (0.48-1.10)	
				– 89.6% of cases and 90.5% of controls did not use vaginal deodorant spray	1.0	
				– 10.4% of cases and 9.5% of controls used vaginal deodorant spray	1.15 (0.85-1.56)	
			–Risk was evaluated based on duration, frequency, and timing of use –Risk was adjusted as above	–86.2% of cases and 88.5% of controls never used powder	1.0	
				Duration of use:		
				–4.1% of cases and 2.9% of controls used powder for 1-9.9 yr	1.39 (0.85-2.28)	
				–3.6% of cases and 2.7% of controls used powder for 10-19.9 yr	1.46 (0.87-2.45)	
				–3.7% of cases and 3.0% of controls used powder for 20-34.9 yr	1.28 (0.78-2.10)	
				–2.3% of cases and 2.9% of controls used powder 35+ yr	0.91 (0.51-1.62)	

(continued)

Table 9. (continued)

Talc/composition	Population/geographical area	Study/diagnosis years	Study description and limitations	Findings	OR or RR (95% CI)	Reference
				Lifetime number of applications:		
				–3.2% of cases and 2.7% of controls reported 1-1599 applications of powder	1.21 (0.71-2.06)	
				–5.6% of cases and 2.8% of controls reported 1600-4799 applications of powder	**2.08 (1.32-3.27)**	
				–2.5% of cases and 3.0% of controls reported 4800-9999 applications of powder	0.87 (0.50-1.53)	
				–2.2% of cases and 2.8% of controls reported 10 000+ applications of powder	0.87 (0.48-1.57)	
				Age at first use:		
				–1.5% of cases and 2.1% of controls were <15 yr old	0.74 (0.37-1.50)	
				–3.3% of cases and 2.7% of controls were 15-20 yr old	1.20 (0.71-2.03)	
				–3.9% of cases and 3.3% of controls were 20-30 yr old	1.25 (0.77-2.03)	
				–5.1% of cases and 3.4% of controls were 30+ yr old	**1.69 (1.08-2.64)**	
				Time since first use:		
				–5.2% of cases and 3.1% of controls reported ≤25 yr	**1.77 (1.12-2.78)**	
				–4.7% of cases and 3.1% of controls reported 25-38 yr	1.46 (0.91-2.32)	
				–2.0% of cases and 2.6% of controls reported 38-45 yr	0.87 (0.47-1.61)	
				–2.0% of cases and 2.7% of controls reported 45+ yr	0.82 (0.44-1.52)	
				Age at last use:		
				–3.1% of cases and 2.5% of controls were <35 yr old	1.14 (0.66-1.97)	
				–4.3% of cases and 3.0% of controls were 35-50 yr old	1.42 (0.88-2.31)	
				–3.1% of cases and 2.7% of controls were 50-60 yr old	1.25 (0.73-2.13)	
				–3.2% of cases and 3.3% of controls were 60+ yr old	1.21 (0.72-2.05)	
				Time since last use:		
				–6.4% of cases and 5.3% of controls are current users	1.30 (0.89-1.91)	
				–3.2% of cases and 2.0% of controls reported ≤12 yr	1.74 (0.98-3.10)	
				–1.7% of cases and 2.16% of controls reported 13-23 yr	0.85 (0.44-1.66)	
				2.3% of cases and 2.1% of controls reported 24+ yr	1.13 (0.61-2.08)	
				Calendar year of first use:		
				–2.3% of cases and 3.0% of controls reported ≤1959	0.86 (0.48-1.53)	
				–3.0% of cases and 2.9% of controls reported 1960-1969	1.10 (0.65-1.89)	
				–3.2% of cases and 2.9% of controls reported 1970-1979	1.12 (0.66-1.89)	
				–5.3% of cases and 2.7% of controls reported 1980+	**2.03 (1.28-3.24)**	
Talc; purity and composition not specified	–902 women from Western PA, Eastern OH, and Western NY in the HOPE study with primary epithelial ovarian, peritoneal, or Fallopian tube cancer –1802 age group- and geography-matched controls	2003-2008	–Patients were asked about reproductive, gynecological, and medical histories, lifestyle, family medical history, whether they ever sought medical attention for fertility issues, use of fertility drugs –Risk was adjusted for race, education, geographical site, BMI, family breast and ovarian cancer history, tubal ligation, OC use, number of live births, breastfeeding, age at menarche, menopausal status, perineal talc use, and HRT use Limitation: –Inability to identify infertile women that never sought medical attention –Reliance on self-reported fertility drug use	Ever/never use of talc:	**OR**	159
				–72.4% of cases and 79.1% of controls reported never using talc in the perineal region	1.0	
				–27.6% of cases and 20.9% of controls reported ever using talc in the perineal region	**1.40 (1.16-1.69)**	

(continued)

Table 9. (continued)

Talc/composition	Population/geographical area	Study/diagnosis years	Study description and limitations	Findings	OR or RR (95% CI)	Reference
Effect of tubal ligation or hysterectomy on risk						
Hospital-based cases/hospital-based controls						
Talc; purity and composition not specified	–211/499 patients at Roswell Park Cancer Institute with epithelial ovarian cancer had tubal ligation or hysterectomy –261/755 age at diagnosis-matched hospital controls had tubal ligation or hysterectomy	October 1982-October 1995	–Described previously	–48.2% of cases and 42% of controls used talc and did not have tubal ligation or hysterectomy –47.4% of cases and 49.8% of controls used talc and had tubal ligation –52% of cases and 60% of controls used talc and had a hysterectomy	**OR** 1.2 (0.8-1.6) 0.8 (0.5-1.2) 0.9 (0.4-2.2)	173
	–135 cases had undergone tubal ligation or hysterectomy within 5 yr of the diagnosis			–Risk excluding these cases	0.9 (0.4-2.2)	
Hospital-based cases/hospital- and population-based controls						
Talcum powder; purity and composition not specified	–188 women from northern California with primary epithelial cancer (from 7 hospitals) –280 matched hospital controls—259 matched pop controls	January 1983-December 1985	–Described previously	–48% of cases and 54% of controls did not use talc –52% of cases and 46% of controls used talc –37% of cases and 34% of controls did not use talc and had no ligation or hysterectomy –38% of cases and 28% of controls used talc and had no ligation or hysterectomy –11% of cases and 20% of controls did not use talc and had ligation or hysterectomy	**OR** 1.0 1.37 (0.97-1.96) 1.0 1.33 (0.58-2.01) *0.50 (0.29-0.88; P < 0.01)*	172
Population-based cases/population-based controls						
Talc; purity and composition not specified	–450 women in the Boston area with epithelial ovarian cancer –454 pop-matched controls (study group combined from Ref[146] and Ref[154]	November 1978-September 1987	–Described previously	–86.6% of cases and 87.7% of controls had no ligation or hysterectomy were talc users –13.4% of cases and 12.3% of controls had tubal ligation or hysterectomy and were talc users –90.0% of cases and 84% of controls had no ligation or hysterectomy were nontalc users –10% of cases and 16% of controls had tubal ligation or hysterectomy and were nontalc users	**OR** 1 1.1 (0.6-2.1) 1 *0.6 (0.4-1.0; P = 0.04)*	147
Talc; purity and composition not specified	–307 registered nurses in 11 states with epithelial ovarian (Nurses' Health Study; described previously)	1982-1996	-Described previously	–Risk for ever talc users that had tubal ligation compared to never talc users –Risk for ever talc use when excluding those with history of tubal ligation or hysterectomy	**RR** 0.97 (0.71-1.32) 1.15 (0.89-1.49)	151
Talc, purity and composition not specified	–450 women from Toronto and Ontario, Canada with epithelial ovarian cancer (pop based) –564 age-matched pop-based controls	November 1989-October 1992	–Study was described previously –Risk with years of after-bath talc use and tubal ligation/hysterectomy was examined –Risk was adjusted as described previously	–Case mean was 28.4 yr and control mean was 26.9 yr of after-bath talc use before ligation/hysterectomy –Case mean was 4.5 yr and control mean was 8.5 yr of after-bath talc use after ligation/hysterectomy	**OR** 1.11 (0.99-1.24) 1.03 (0.82-1.29)	143
Talc; purity and composition not specified	–256 women from 22 central CA counties with epithelial ovarian cancer (pop based) –1122 age- and ethnicity-matched controls	2000-2001	–Study was described previously –Risk of talc use and hysterectomy or tubal ligation was examined Risk was adjusted as described previously	Tubal ligation: –57.4% of cases and 65.8% of controls did not have tubal ligation and never used talc 42.6% of cases and 34.2% of controls did not have tubal ligation and ever used talc –56.9% of cases and 54.9% of controls did have tubal ligation and never used talc –43.1% of cases and 45.1% of controls did have tubal ligation and ever used talc	**OR** 1.0 **1.54 (1.10-2.16)** 1.0 0.88 (0.46-1.68)	162

(continued)

Table 9. (continued)

Talc/composition	Population/geographical area	Study/diagnosis years	Study description and limitations	Findings	OR or RR (95% CI)	Reference
				Hysterectomy: –59.5% of cases and 63.7% of controls did not have a hysterectomy and never used talc –40.5% of cases and 36.3% of controls did not a hysterectomy and ever used talc –50.0% of cases and 58.8% of controls did have a hysterectomy and never used talc –50.0% of cases and 41.2% of controls did have a hysterectomy and ever used talc	1.0 1.33 (0.95-1.87) 1.0 1.79 (0.91-3.52)	
Talc; purity and composition not specified	–1576 women from Australia with epithelial ovarian cancer –1509 age- and state of residence-matched pop controls	January 2002-September 2005	–Study was described previously Risk was examined with number of years talc use posthysterectomy or tubal ligation	–88% cases and 88% controls reported no talc use postsurgery 3.3% of cases and 3.3% of controls reported 0-10 yr talc use –5.5% of cases and 5.7% of controls reported >10-25 yr talc use –3.1% of cases and 3.0% of controls reported >25 yr talc use –Trend	**OR** 1.0 1.08 (0.71-1.62) 1.14 (0.82-1.57) 1.00 (0.64-1.51) P = 0.61	161
Occupational exposure and risk						
Talc used as a coating agent for paper; purity and composition not specified; workers may also have been exposed to asbestos and/or other dusts	–46 female pulp and paper workers from 10 mills in Norway with epithelial ovarian cancer –179 age-matched controls identified by incidence density sampling	1953-1999 (mostly from 1980+)	–Risk estimates specific to mill, work department, agent, and time period –Indicators of occupational exposure included duration of employment, time since first exposure to diagnosis, and year of first exposure –Patients were asked about occupational history, possible household asbestos exposure, fertility pattern, age at menarche and menopause, OC use, family cancer history, and other personal factors Limitations: –There were many missing values for the question on hygienic talc use	–50% of cases and 52% of controls reported never being exposed to talc –50% of cases and 48% of controls reported ever being exposed to talc	**OR** 1.0 1.10 (0.56-2.18)	160
Talc; purity and composition not specified	–275 women in the Washington, DC area with epithelial ovarian cancer (hospital based) –316 hospital age- and race-matched controls	1978-1981	–RR of ovarian cancer was determined according to length of occupational exposure to talc within various occupations –Exposure = # of years in the job assigned probabilities of definite, probable, and possible exposure –Risk was adjusted for employment, race, age, parity, and gynecologic surgery Limitation: –No information was available on individual exposure characteristics, leading to the assumption that it was homogenous within job title	–95.7% of cases and 90.2% of controls were not exposed –1.8% of cases and 3.5% of controls were exposed for <5 yr –0.7% of cases and 2.5% of controls were exposed for 5-9 yr –1.8% of cases and 3.8% of controls were exposed for 10+ yr	**RR** 1.0 0.5 (0.1-1.4) 0.3 (0.1-1.4) 0.5 (0.2-1.5)	156
Endometrial cancer						
Talc; purity and composition not specified	–599 of 66 028 women from the Nurses' Health Study with invasive endometrial adenocarcinoma	1982-2004	–Described previously –Risk was assessed among all women –Risk was adjusted for age, parity age at last birth, menarche, and menopause, OC and PMH use, BMI, smoking, diabetes, menopausal status, and family history of uterine cancer Limitations: –Single assessment of talc use (ever/never) –Did not assess duration of talc use	Use of talc: –55.8% of cases reported never using talc perineally –44.2% of cases reported ever using talc perineally –66.3% of cases reported no regular perineal use of talc (1+/wk) –33.7% of cases reported regular perineal use of talc	**IRR** 1.0 1.13 (0.96-1.33) 1.0 1.17 (0.99-1.40)	158

(continued)

Table 9. (continued)

Talc/composition	Population/geographical area	Study/diagnosis years	Study description and limitations	Findings	OR or RR (95% CI)	Reference
			–Risk assessed in premenopausal women (70 cases [11.7% of all women] were premenopausal) –Risk was adjusted for age, parity, age at last birth, age at menarche, OC use, BMI, smoking, diabetes, and family history of uterine cancer –Risk was assessed among postmenopausal women (529 cases [88.3% of all women] were postmenopausal) –Risk estimate was multivariate (as for all women) or adjusted by age	Talc use in premenopausal women:		
				–67.1% of cases reported never using talc perineally	1.0	
				–32.9% of cases reported ever using talc perineally	0.69 (0.40-1.19)	
				–75.7% of cases reported no regular perineal use of talc (1+/wk)	1.0	
				–24.3% of cases reported regular perineal use of talc	0.77 (0.42-1.39)	
				Talc use in postmenopausal women:	Multivariate:	
				–54.3% of cases reported never using talc perineally	1.0	
				–45.7% of cases reported ever using talc perineally	**1.21 (1.02-1.44)**	
				–65% of cases reported no regular perineal use of talc (1+/wk)	1.0	
				–35% of cases reported regular perineal use of talc	**1.24 (1.03-1.48)**	
					Age-adjusted:	
				As above	1.0	
					1.38 (1.16-1.64)	
					1.0	
					1.40 ((1.17-1.68)	
			–Risk in postmenopausal women based on frequency of use and application to sanitary napkins –Risk was adjusted multivariate (as above) or by age	Frequency of use	Multivariate:	
				10.8% of cases reported perineal use of talc <1×/wk	1.09 (0.81-1.45)	
				16.4% of cases reported perineal use of talc 1-6×/wk	1.28 (1.00-1.63)	
				18.5% of cases reported daily use of talc	1.24 (0.98-1.56)	
					Age adjusted:	
				As above	1.22 (0.91-1.62)	
					1.40 (1.10-1.79)	
					1.49 (1.18-1.87)	
				Sanitary napkin talc use:	Multivariate:	
				–85.7% of cases never used talc on sanitary napkins	1.0	
				–14.3% of controls used talc on sanitary napkins	0.98 (0.75-1.27)	
				As above	Age adjusted:	
					1.0	
					1.04 (0.80-1.35)	
Talc; purity and composition not specified	–1399 women in Australia with primary endometrial cancer (pop based) –740 controls	July 2005-December 2007	–Patients were asked about medical, hormonal, and reproductive histories, other potential risk factors, and talc use –Risk was adjusted for age, age at menarche, parity, pregnancies, OC use, hormone replacement therapy, BMI, and smoking status Limitation: –Nonparticipation, in that those who did not participate may have more advanced disease –Nondifferential misclassification of talc use –Residual confounding may have distorted the results	Use of talc:	**OR**	164
				–40.7% of cases and 41.5% of controls never used talc	1.0	
				–59.3% of cases and 58.5% of controls ever perineal talc use	0.88 (0.68-1.14)	
				–71.9% of cases and 70.4% of controls reported ever upper body use	0.9 (0.71-1.14)	
				Frequency of any perineal talc use:	0.68 (0.40-1.15)	
				–5.1% of cases and 7.1% of controls reported infrequent use	0.88 (0.56-1.41)	
				–9.1% of cases and 8.5% of controls reported use a few times/mo	1.32 (0.82-1.11)	
				–11% of cases and 7.1% of controls reported use a few times/wk	0.82 (0.61-1.14)	
				–33.3% of cases and 35% of controls reported daily use	0.44	
				–P_{trend} (including nontalc users)		
				Duration of any perineal talc use:		
				–19% of cases and 16% of controls reported 1-20 yr use	1.21 (0.84-1.75)	
				–15.6% of cases and 11.2% of controls reported 21-40 yr use	1.1 (0.73-1.65)	
				–18.2% of cases and 18.8% of controls reported 41-60 yr use	0.82 (0.57-1.17)	
				–5% of cases and 11.2% of controls reported 61-80 yr use	0.25 (0.15-0.43)	
				–P_{trend} (including nontalc users)	*<0.001*	
				Frequency of any upper body talc use:		
				–4.4% of cases and 6.6% of controls reported infrequent use	0.57 (0.35-0.93)	
				–6.9% of cases and 9.1% of controls reported use a few times/mo	0.58 (0.38-0.89)	
				–15.4% of cases and 10.1% of controls reported use a few times/wk	**1.45 (1.01-2.09)**	
				–45.1% of cases and 44.3% of controls reported daily use	0.9 (0.70-1.16)	
				–Trend (including nontalc users)		

(continued)

Table 9. (continued)

Talc/composition	Population/geographical area	Study/diagnosis years	Study description and limitations	Findings	OR or RR (95% CI)	Reference
				Duration of any upper body talc use:		
				–20.7% of cases and 19.4% of controls reported 1-20 yr use	1.16 (0.85-1.58)	
				–16.9% of cases and 12.8% of controls reported 21-40 yr use	1.12 (0.79-1.59)	
				–23.6% of cases and 22.6% of controls reported 41-60 yr use	0.86 (0.64-1.17)	
				–9.3% of cases and 14% of controls re	0.41 (0.28-0.61)	
				–ported 61-80 yr use	*0.001*	
				–P_{trend} (including nontalc users)		
			–Risk was evaluated using a "composite" variable that multiplied frequency of talc use by years of use to assess lifetime exposure –Resulting values were categorized as low (<5 yr); moderate (5-20 yr); high (20-40 yr); very high use (40+ yr)	Perineal talc use:		
				–16.6% of cases and 15.6% of controls had low lifetime use	0.95 (0.65-1.37)	
				–12% of cases and 11.4% of controls had moderate lifetime use	1.0 (0.66-1.54)	
				–11.2% of cases and 8.6% of controls had high lifetime use	1.01 (0.64-1.60)	
				–17.2% of cases and 20.9% of controls had very high lifetime use	0.67 (0.47-0.96)	
				–P_{trend} (including nontalc users)	0.07	
				Upper body talc use:		
				–13.5% of cases and 17% of controls had low lifetime use	0.72 (0.52-1.01)	
				–14.7% of cases and 13% of controls had moderate lifetime use	1.25 (0.87-1.78)	
				–16.5% of cases and 12.6% of controls had high lifetime use	1.07 (0.75-1.52)	
				–25.8% of cases and 25.9% of controls had very high lifetime use	0.8 (0.59-1.07)	
				–P_{trend} (including nontalc users)	0.49	

Abbreviations: BMI, body mass index; CI, confidence interval; CLE, cumulative lifetime exposure; HOPE, Hormone and Ovarian Cancer Prediction; HRT, hormone replacement therapy; IRR, incidence rate ratios; NECC, New England Case Control; NSAID, nonsteroidal anti-inflammatory drug; OC, oral contraceptive; OR, odds ratio; PMH, postmenopausal hormone; pop, population; RR, relative risk.
[a]Bolded text was used to highlight statistically significant increases. Italicized text was used to highlight statistically significant decreases.

Table 10. Summary of Case–Control Studies Evaluating Ovarian Cancer Risk for "Ever" Use of Talc in the Perineal Area.

# Case subject	# Control subjects	Study years	P/H cases	OR or RR	95% CI	Reference
Hospital-based cases						
135	171	1974-1977	H	0.7	0.4-1.1	155
215	215	1978-1981	H	**1.92**	**1.27-2.89**	146
77	46	1981-1985	H	1.7	0.7-3.9	167
499	755	1982-1995	H	1.0	0.8-1.3	173
235	239	1984-1987	H	1.5	1.0-2.1	154
189	200	1989-1991	H	1.05	0.28-3.98	170
767	1367	1994-1998	H	1.5	1.1-2.0	165
153	101	1995-1996	H	2.49	0.94-6.58	152
Population-based cases						
116	158	1980-1985	P	1.1	0.7-2.1	153
112	224	1984-1986	P	3.9	0.9-10.6	144
313	422	1986-1988	P	**1.5**	**1.1-2.0**	145
450	564	1989-1992	P	**1.42**	**1.08-1.86**	143
824	860	1990-1993	P	**1.27**	**1.04-1.54**	166
563	523	1992-1997	P	**1.60**	**1.18-2.15**	148
668	721	1998-2003	P	1.16	0.90-1.49	149
609	688	1998-2002	P	**1.48**	**1.15-1.91**	174
83	134	1998-2008	P	1.19	0.68-2.09	163
550	553	1998-2008	P	1.04	0.82-1.33	163
256	1122	2000-2001	P	**1.37**	**1.02-1.85**	162
1576	1509	2002-2005	P	**1.17**	**1.01-1.36**	161
363	752	2002-2005	P	1.10	0.84-1.45	157
902	1802	2003-2008	P	**1.40**	**1.16-1.69**	159

Abbreviations: CI, confidence interval; H, hospital; OR, odds ratio; P, population; RR, relative risk.
Note: Bolded text was used to highlight confidence intervals >1.

Among the epidemiological investigations reporting statistically significant associations, the RR estimates ranged between 1.0 and 2.0 and were barely statistically significant (Tables 9 and 10; Figure 2). For such low estimates, epidemiological methods generally cannot distinguish causality from even minor confounding risk factors or biases.[188-191] Age, race, low parity, infertility, and a family history of ovarian, endometrial or breast cancer are among the most likely risk factors in the etiology of epithelial ovarian cancer.[12,192] Others have suggested that the effects of cancer treatment, smoking, and consuming coffee regularly could explain the small increases in the RR estimates reported for ovarian cancer in women using cosmetic talc products perineally.[172,193,194] Many physiological, sociological, and exposure factors have been linked to ovarian cancer, a number of them with a stronger association than the hygienic use of cosmetic talc, but causality has not been established for any of them.[182] The etiology of the majority of ovarian cancer cases is still unknown.

Prospective cohort studies do not suffer from recall bias because the exposures are recorded before the cancers were diagnosed. The single cohort study available found no statistically significantly association between perineal talc use and all ovarian cancer subtypes combined but did report such an association with invasive serous ovarian cancer (RR = 1.4; 95% CI: 1.02-1.91)[151] The odds ratios for serous ovarian cancer were also elevated in several case–control studies.[143,148,154,173] All of the odds ratio estimates reported in these studies were less than 1.7.

Talc exposure probably varies over time as women age and their reasons for deciding to use talc change. Talc use might be sporadic, seasonal, or change with circumstances (eg, sexual activity and parity). However, no studies have characterized either the feminine hygiene habits involving the use of cosmetic talc products in the general population or the latency of purported talc-induced ovarian cancer to enable resolving these issues.[190] Moreover, the epidemiological studies used questionnaires that did not focus specifically on the patients' use of talc or talcum powders, as distinct from nontalc powders or sprays of known (eg, corn–starch based) or unknown compositions.[177] It is not clear that all of the patients understood the distinction between talc or talcum powders and talc-free powders when answering the questions. These factors contribute substantially to the uncertainties associated with the risk estimates of the prospective study as well as the case–control studies.

An early meta-analysis found a statistically significant adjusted pooled odds ratio of 1.27 (95% CI: 1.09-1.48) for ovarian cancer in women who ever used talc in the perineal or abdominal region compared to women who never used talc[195] However, the authors cautioned that this result does not provide the basis for inferring causality because many of the studies had substantial design limitations.

A more recent meta-analysis yielded a statistically significant overall summary RR of 1.33 (95% CI: 1.16-1.45).[194,196] However, sensitivity analyses revealed clear differences in outcome based on study design. Population-based case–control studies yielded a statistically significant increase in the risk of ovarian cancer for hygienic use of talc, but hospital-based case–control studies showed no statistically significant difference.

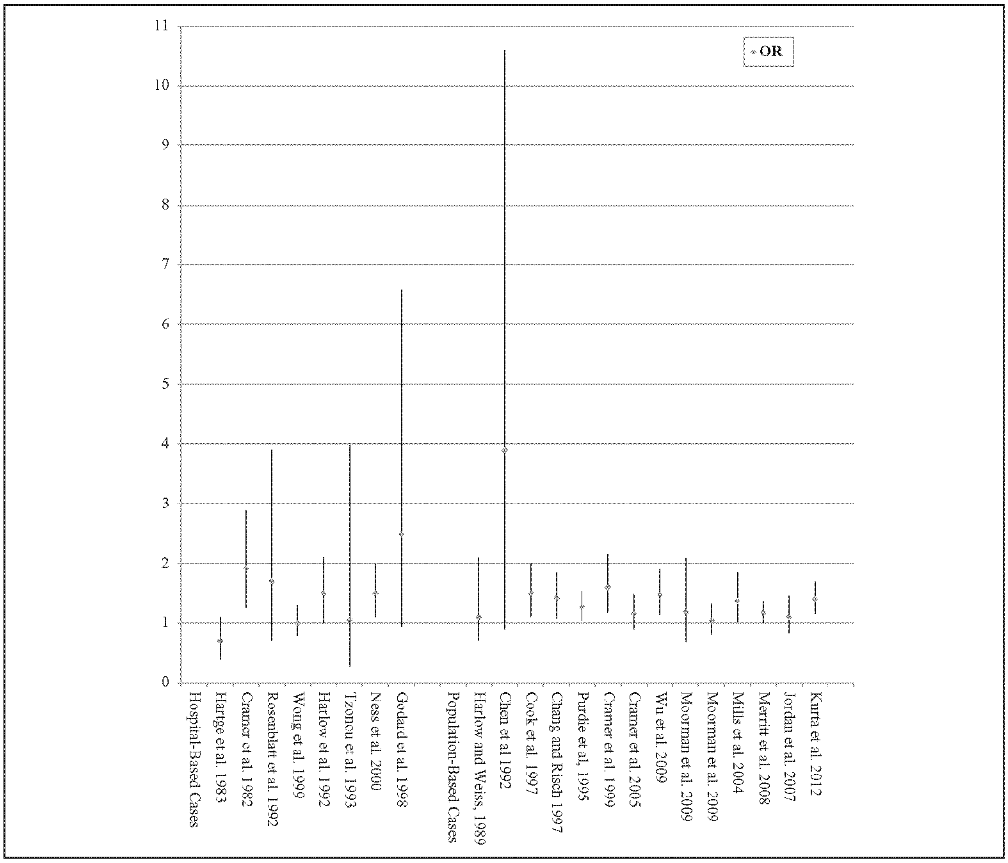

Figure 2. Odds ratio and confidence intervals in case–control studies evaluating ovarian cancer risk for "ever" use of talc in the perineal area. References[143-146,148,149,152-155,157,159,161-163,165-167,170,173,174].

There were no differences in the frequency of talc use in the respective control groups. The authors suggested that the difference in outcomes may be attributable to a bias, such as a "treatment effect" among the cases (ie, side effects from treatments for ovarian cancer may make talc use more likely in the patients than in the controls).

A still more recent meta-analysis reported a statistically significant overall summary RR of 1.35 (95% CI: 1.26-1.46).[194,197] However, a statistical test for data heterogeneity indicated substantial inconsistencies among the pooled studies and an invalid pooled summary RR estimate. Thus, the outcome provided no support for a causal association between perineal talc use and ovarian cancer.[188,198]

Most of the epidemiological studies found no trend of increasing ovarian cancer risk with increasing exposure duration or frequency or cumulative exposure, despite a 5-fold difference between the lowest and the highest exposure groups (Table 10).[199] Several of these studies reported an apparent inverse trend.[142,143,148,151,196,200] In 1 study, suggestions of an exposure-effect relationship were obtained only after excluding exposures during pregnancy, during oral contraceptive use, and after sterilization.[148] Overall, however, the results of the epidemiological studies are not consistent with known mechanisms of carcinogenesis, which would be expected to yield positive exposure-effect trends. The inverse trends, in particular, are not compatible with a causal relationship between perineal talc exposure and ovarian cancer.[193,196]

No plausible biological mechanism has been identified to explain how exposure to talc containing no asbestos or other asbestiform fibers could cause ovarian cancer. If perineal talc

use can cause ovarian cancer in a dose-dependent manner, then there should be also be associations between such talc use and both cervical and uterine cancers, where talc exposure would be expected to be greater than ovarian exposure. No such associations have been reported.

Thirty or more years ago, cosmetic talc was thought to contain substantial amounts of asbestos fibers,[23,201] which would clearly represent a carcinogenic risk. However, FDA and IARC found that this contention could not be substantiated.[18,38,201-204] Further, stringent quality criteria have been in place for cosmetic talc since 1976.[205] Meeting these criteria requires the elimination of detectable asbestos and other asbestiform fibers. Thus, the increased ovarian cancer risks associated with cosmetic talc use reported in some of the more recent epidemiological studies have generally not been attributed to contamination with asbestiform fibers.

However, the potential carcinogenicity of talc has been attributed by some authors to the chemical similarity of talc to asbestos. Both substances are magnesium silicates, but they share no other characteristics in common.[12,22,205] The aspect ratio of the fibrils is generally considered to be critical for the carcinogenicity of asbestos. In contrast, talc consists of 3-layer silica–brucite–silica sheets stacked together to form small platy packets with highly insoluble, hydrophobic surfaces. Cosmetic talc does not contain fibrils.

Alternatively, some researchers have suggested that talc in the ovaries could cause cancer, indirectly, through a talc-induced inflammatory response, analogous to the action of asbestos fibers in the lungs.[206] However, pelvic inflammatory diseases, such as endometriosis, peritonitis, and tubo-ovarian abscess formation, have not been found to be associated with increased risks of ovarian cancer. In addition, anti-inflammatory drug use did not reduce ovarian cancer risk estimates in several studies.[161,207]

Most recently, 1 group proposed that elevated expression of anti-MUC1 antibodies induced by perineal talc in the peritoneal lymph nodes might explain the reported associations between talc exposure and ovarian cancer.[149] However, the application of talc powder to other parts of the body appears to induce anti-MUC1 antibody expression as well, and elevated anti-MUC1 antibody levels generally have not been associated with increased risks of ovarian cancer. Thus, this proposal remains highly speculative.

Talc is commonly used clinically as the active agent for pleurodesis. This procedure involves introducing a talc slurry directly into the pleural space to induce fibrogenesis. No increase in the incidences of lung or pleural cancers has been found in multiple clinical studies involving hundreds of patients followed for decades after pleurodesis.[193,208,209]

The results of these clinical studies are consistent with epidemiological investigations reporting no statistically significant increase in mortality from lung cancer or mesothelioma in workers occupationally exposed to "pure" talc.[92,95,97] As stated by 1 author, "the likelihood that talc could selectively induce ovarian cancer and not lung cancer at exposure concentrations orders of magnitude lower than that experienced in occupational settings, argue against its toxicity."[22] Others have noted the absence of reports suggesting that talc inhalation is associated with either lung cancers or mesothelioma in consumers[12].

Accordingly, animal cancer bioassays using rodents exposed to high concentrations of talc in air indicate that talc is not a primary carcinogen. The NTP life-time inhalation carcinogenesis bioassay found no ovarian lesions in female mice or rats and no malignant respiratory-tract lesions in male rats or male or female mice.[10] Further, the lung cancers found in female rats can be plausibly attributed to chronic pulmonary particle overload, rather than to the possible carcinogenicity of talc.[124,210] The use of micronized talc in the NTP study probably contributed to the pulmonary overloading. This interpretation is supported by the results of an earlier lifetime inhalation study in hamsters. The animals were exposed to a talc baby powder aerosol at rates that exceeded those measured in infant-dusting simulations (mg h/m^3) by 30- to 1700-fold.[12,82] The exposures had no effect on the type, incidence, or degree of histopathological findings in the lungs or other tissues examined, or on body weight, survival, or any other parameter evaluated, compared with the sham-exposed controls.

Further, the injection of talc into ovarian bursa of rats in 1 study (100 μL/ovary of 100 mg 0.4 to 14 μm platy talc crystals/mL buffered saline) induced no cancers.[68]

In summary, critical issues that call into question the validity of the statistically significant associations reported in some of the epidemiological studies include:

- absence of persuasive evidence that talc can migrate from the perineum to the ovaries;
- lack of consistent statistically significant positive associations across studies;
- uniformly small RR estimates in studies reporting positive associations;
- failure to rule out plausible alternative explanations of the statistically significant results, including biases, confounding risk factors, and exposure misclassifications;
- absence of statistically significant associations between ovarian cancer and using talc-dusted diaphragms or condoms;
- overall lack of positive exposure-effect relationships;
- inverse trends for both duration of use and frequency of use in some studies;
- absence of a plausible biologic mechanism; and
- lack of credible, defensible evidence of carcinogenicity from the results of epidemiological studies of occupational exposures and animal bioassays.

Irritation and Sensitization

Sensitization

Nonhuman. Talc was not a sensitizer in female Hartley guinea pigs.[211] Female Hartley guinea pigs (number not stated) received an intradermal injection of 10 mg sterile talc in an emulsion of 0.5 mL sterile saline and 0.5 mL Freund complete

adjuvant; 6 guinea pigs were dosed in the same manner with 10 mg starch glove powder. (Chemical characterization data were not provided; the talc was British Pharmacopeia grade). Eleven control animals were injected with the emulsion only. Skin tests were then performed at various intervals by challenging all animals with suspensions of starch glove powder in one ear and talc in the other. Slight cutaneous thickening was observed in all control animals 24 hours after challenge with both suspensions, and the responses were similar to both talc and the starch. The response to challenge with talc in the talc test group was similar to that seen in the controls. Animals in the starch group had a statistically significantly greater response to the starch challenge compared to the controls.

Summary

Talc is a sheet silicate that belongs to the silicate subclass phyllosilicates. In its purest form, it is a mineral that corresponds to the chemical formula of hydrous magnesium silicate; commercially, it contains varying amounts of other minerals naturally found in the ore. Only talc containing no detectable fibrous, asbestos minerals is used in cosmetics, and cosmetic talc must consist of a minimum of 90% hydrated magnesium silicate, with the remainder consisting of naturally associated minerals such as calcite, chlorite, dolomite, kaolin, and magnesite.

In 2013, FDA VCRP data indicated that talc was used in 3469 cosmetic formulations and, according to concentration of use data received in response to a Council survey, talc is used at up to 100% in cosmetic formulations. Talc is used in almost every category of cosmetic product and it is used in products that may be applied to baby skin, products that could be incidentally ingested, products used near the eye area or mucous membranes, and in products that are sprayed. The particle size of talc raw material varies widely by product type and by manufacturer, although typical cosmetic talcs are reported to have average particle sizes ranging between 4 and 15 μm when measured by sedimentation method.

Talc has many commercial uses and it has pharmaceutical use. It is used as a color additive in drugs and is exempt from certification. Sterile talc is approved as a sclerosing agent. Talc is not allowed for use on the surface of medical gloves. It is used in the production of foods, and it is approved as an indirect food additive as a color.

Syrian golden hamsters received a single 2-hour nose-only exposure to talc tested as a commercial baby powder (chemical characteristics unknown), with a median aerodynamic diameter of 6.4 to 6.9 μm. The biological half-life of the talc deposited in the lungs was 7 to 10 days. No translocation from the respiratory tract to other tissues was found in this study, and the clearance of talc from the lungs was complete within 4 months after exposure. Following oral administration of [^{3}H]talc to mice, rats, and guinea pigs, most of the radioactivity was excreted in the feces. Wistar rats were used to determine the systemic distribution of talc following intrapleural administration; the study suggested that talc is absorbed very rapidly through the pleura, reaching the systemic circulation with deposition in other organs within 24 hours of administration, and that the distribution is not dose related.

The acute oral LD_{50} of rats was 920 mg/kg bw in one study and >5000 mg/kg bw in another. In a study in which mice were placed in a box with circulated baby powder, the mice removed after 30 or 60 minutes recovered completely and the mice removed after 90 or 120 minutes died; the chemical composition, amount of powder, and size of the box were not specified. In rats dosed with a single bilateral injection of 100 mg/mL talc into the ovarian bursa and killed 1 to 18 months after dosing, one or both ovaries of rats dosed with talc were cystic in appearance at all time periods; the cystic structures were attributed to distention of the bursal sac. Foreign body granulomas, without surrounding inflammation, were seen in the cortical area of 5 of the injected ovaries, and talc was observed in the granulomas. In rats, a granulomatous reaction in which foreign-body giant cells containing refractile materials was observed without fibrosis at 1 and 3 months after a single ip injection of 50 mg/kg bw nonfibrous talc. In rats dosed with a single ip injection of 0.02, 0.1, or 0.5 g talc in 5 mL normal saline, clusters of foci of inflammatory cells were observed scattered on the surface of the peritoneum, and talc particles were seen in the center of each focus.

There were no remarkable results found in studies examining the cellular effect of talc, such as cytotoxicity assays, assays examining the effect of talc on cell viability, or studies on the induction of apoptosis (among others).

Dermal application of talc to shaved rabbit skin for 6 weeks resulted in dryness of the skin and skin erosion. Oral administration to rats for 5 days produced minimal toxicity. In inhalation studies, exposure of mice and rats for 4 weeks (25 μm particle size) resulted in macrophages in the alveolar space, with more found in the mice than in the rats. In rats exposed for 3, 6, or 12 months, minimal to slight fibrosis resulted. In hamsters, exposure to baby powder (95% talc; 4.9-6.0 μmol/L) did not result in clinical toxicity, and no trends were observed. Intrapleural administration of talc (25 μm) to rats did not result in mesotheliomas; granulomas at the injection site were common. Infections occurred, but no neoplastic or perineal changes, when talc was instilled intravaginally or perineally in rats. Upon iv injection of talc (<5 μm) once weekly for 3 weeks, talc was found in the lungs and in the liver throughout the study.

Talc is non- or slightly irritating to rabbit eyes. In a female patient who presented with a foreign body sensation and inflammation of the conjunctiva of both eyes, a diagnosis of foreign body granuloma secondary to talc was made. Application of talc to wounded skin can give rise to scab formation, possible infection, and foreign body granulomas in the dermis.

Talc has a TLV (respirable fraction) of 2 mg/m^3 as a TWA. Human pulmonary effects of talc include diffuse interstitial fibrosis and progressive massive fibrosis (often called complicated pneumoconiosis). In occupational exposure studies, statistically significantly elevated SMRs for silicosis and silicotuberculosis were observed in an early study of talc miners and

millers in the Italian Piedmont region exposed to talc that contained no fibrous material except for tremolite micro-inclusions; SMRs were statistically significantly reduced for malignant neoplasms, including lung, bronchial, and tracheal cancers. A follow-up of this group found statistically significant increases in mortality, which were attributed primarily to nonmalignant respiratory diseases among the miners. A cohort study of talc miners and millers exposed to talc and magnesite containing trace amounts of quartz, tremolite, and anthophylite found no statistically significant SMRs for all causes, all cancers, or diseases of the circulatory system or respiratory tract. The results of several other epidemiological studies were likely confounded by the presence of up to 3% silica or 6% actinolite in the talc, exposures to high concentrations of silica with or without exposures to fibrous talc (tremolite), or concurrent exposures to radon daughters. A meta-analysis of studies of miners and millers who worked with nonasbestiform talc reported summary SMRs for lung cancer of 0.92 (95% CI: 0.67-1.25) for millers in 5 countries exposed to high levels of talc without exposure to other occupational carcinogens, and 1.2 (95% CI: 0.86-1.63) for miners in 3 countries exposed to high levels of talc as well as to silica or radon and radon daughters. Studies examining radiological, lung-functional, and clinical parameters in talc miners and millers and rubber workers found some statistically significant changes.

In exposure-during-cosmetic use studies, the researchers noted that there was a wide variation in talcing times and methods, often by the same volunteer during different applications. Reported talcing times ranged from 17 to 31 seconds. Endobronchitis and airway stricture were reported in one case in which a patient applied large amounts of talc powder to her face. In another case, a chronic pulmonary granulomatous reaction was reported in a patient who applied "nonpowdering talc" to her face for 20 years, followed by use of talcum powder 2 to 3 times a day for a 10-year period.

Talc administered orally as a suspension in corn oil was not a developmental toxicant in mice (16-1600 mg/kg bw on days 6-15 of gestation), rats (16-1600 mg/kg bw on days 6-15 of gestation), hamsters (12-1200 mg/kg bw on days 6-10 of gestation), or rabbits (9-900 mg/kg bw on days 6-18 of gestation). No dose–response or time-trend pattern was observed in rats that received a single oral dose or once daily dose for 5 days of 30 to 5000 mg/kg bw talc.

In vitro, talc was not genotoxic in an UDS assay (10, 20, or 50 $\mu g/cm^2$) or an SCE assay (2, 5, 10, and 15 $\mu g/cm^2$) in RPMCs. Talc was not genotoxic in a host-mediated assay in mice dosed by gavage with a single dose or once daily for 5 days with 30, 300, 3000, or 5000 mg/kg bw talc or cytogenetic assay in rats dosed by gavage once daily for 5 days with 30, 300, 3000, or 5000 mg/kg bw talc. Talc was also not genotoxic in a dominant lethal assay in which rats were dosed by gavage with a single dose or once daily for 5 days with 30, 300, 3000, or 5000 mg/kg bw talc.

In a lifetime inhalation study, a carcinogenic effect was not observed upon exposure of hamsters to a commercial baby powder containing 95% platy talc for 30 or 150 min/d, 5 days/wk. A bioassay using mice and rats was performed by the NTP to determine the carcinogenic potential of nonasbestiform, cosmetic-grade micro-talc following exposure by inhalation, and it was concluded there was *no evidence of carcinogenic activity* in male or female $B6C3F_1$ mice, *some evidence of carcinogenic activity* in male F344/rats, and *clear evidence of carcinogenic activity* in female F344/N rats. The mice were exposed to 6 mg/m^3 (MMAD 3.3 $\pm$ 1.9 μm) or 18 mg/m^3 (MMAD 3.6 $\pm$ 2.0 μm) talc for 6 h/d, 5 days/wk, for 103 to 104 weeks. The rats were exposed to 6 mg/m^3 (MMAD 2.7 $\pm$ 1.9 μm) or 18 mg/m^3 (MMAD 3.2 $\pm$ 1.9 μm) talc for 6 h/d, 5 days/wk, for 113 weeks (males) or 122 weeks (females). Concerns have been raised about this study, including concerns that micronized talc having a significantly smaller particle size distribution than cosmetic talc was used, aerosol concentrations were not properly controlled, proper procedures for dose selection were not followed resulting in the MTD being exceeded at both concentrations tested, and particle overload in the lungs was most likely the cause of the adverse effects reported.

Talc did not induce pleural tumors in rats following intrapleural injection of 20 mg talc (mean size 2.6 $\pm$ 2.3 μm). Few tumors developed in rats given weekly ip injections of 25 mg talc suspended in 2 mL saline weekly for 4 weeks. In mice given an ip injection of 20 mg of UV-sterilized commercial talc in 1 mL saline, 12.5% of the animals developed mesothelioma. The researchers also examined the effects of administering 3 mg talc + 3 mg B[a]P in 0.2 mL saline to hamsters in both studies, concluding that talc + B[a]P had a cocarcinogenic effect; however the Panel noted that appropriate controls were not used.

Results of studies examining particulate migration in the genital tract have been mixed. In one study using monkeys, there was no translocation of bone black from the vagina to the oviducts. However in a human study, researchers concluded that there was evidence of migration of carbon particles to the uterus or the Fallopian tubes and ovaries, although other researchers stated that this finding is misleading because only 1 radioactive label was used. In a study in rabbits, the number of large starch particles in peritoneal cavity rinsate was greater in test groups that were exposed intravaginally to glove lubricant (ie, starch) than in controls. In humans, it appeared that starch particles migrated to the cervix and uterus.

In studies specific to talc migration, mixed results have also been reported. In rats, talc was found in the ovaries of rats dosed intrauterinally with talc; in rats exposed with a single intravaginal dose, talc was found in the ovaries 4 days after dosing, but not 24 or 48 hours after dosing. Talc was not found in the ovaries of rabbits given 6 daily intravaginal doses, and there was no translocation of talc from the vaginas of monkeys to the ovaries, oviducts, or the body of the uterus. In humans, talc particles were found in 10 of 13 ovarian tumors and 12 of 21 cervical tumors; the particles found in the ovarian tumors were generally smaller than those in the cervical tumors, that is, 1000 Å to 2 μm versus up to 5 μm, respectively. In women with benign ovarian neoplasms, half of whom applied talc to the perineum or underwear, there was no linear relationship

between ovarian talc powder burden and exposure. Electron microscopy counts were 0 for about half of the patients exposed to talc as well as half of the controls; talc was observed with light microscopy in all patients exposed to talc and 11 of 12 controls.

Numerous epidemiological studies have been performed examining the risk of ovarian cancer following talc exposure. Among the epidemiological investigations reporting statistically significant associations, the RR estimates ranged between 1.0 and 2.0 and were barely statistically significant. Many physiological, sociological, and exposure factors have been linked to ovarian cancer, a number of them with a stronger association than that of hygienic use of cosmetic talc, but causality has not been established for any of them. Most of the epidemiological studies found no trend of increasing ovarian cancer risk with increasing exposure duration or frequency or cumulative exposure, despite a 5-fold difference between the lowest and the highest exposure groups. Several of these studies reported an apparent inverse trend. The results of several epidemiological studies suggested that medical procedures expected to prevent the translocation of talc to the ovaries, such as tubal ligation or hysterectomy, reduce the RR estimates associated with talc use. Other studies found no difference in RR between women who had tubal ligation or hysterectomy and women who did not have these procedures. One study reported inverse exposure-effect trends with duration of talc exposure after adjusting for tubal ligation. The use of talc-dusted condoms or diaphragms (including diaphragms known to have been stored in talc powder), which would clearly result in exposure close to the cervical opening, was not associated with an increased estimate of RR of ovarian cancer. Talc was not a sensitizer in female Hartley guinea pigs.

Discussion

The safety of talc has been the subject of much debate through the years, partly because the relationship between talc and asbestos is commonly misunderstood. Often in early studies, some of the analytical methods used to identify asbestos in talc were not performed and/or interpreted correctly, leading to incorrect conclusions that high levels of asbestos were present in talc. In 1976, the CTFA issued stringent purity standards for talc used in cosmetics, including specifications that talc must contain no detectable fibrous, asbestos mineral; generally accepted methods for the determination of asbestiform amphibole minerals in cosmetic talc were also identified by the CTFA. Therefore, the CIR Expert Panel evaluated the safety of only talc that does not contain detectable fibrous, asbestos minerals.

During its deliberations, the Panel discussed a 2012 FDA study, in which talc samples and talc-containing products were analyzed for the presence of asbestos. Of the 9 companies contacted, 4 supplied data to the FDA. No asbestos was detected in any of the talc samples or the talc-containing products. The Panel requested clarification of the analytical methods used to confirm lack of significant asbestiform amphibole content. In response to this request, the Panel was advised that talc is certified to be asbestos free, and their mines are monitored for asbestos concentrations. The Panel received documentation from industry of the analytical methods used to confirm the purity of talc, particularly with respect to contamination by asbestos, quartz, and other inorganics. The analysis protocol, which is standardized in CFTA Method J 4-1, employs X-ray diffraction and polarizing light microscopy to detect asbestos fibers at levels below 0.05%.

As evidenced in this safety assessment, numerous studies have been performed to investigate whether or not a causative relationship exists between the cosmetic use of talc in the perineal area and ovarian cancer. The Panel reviewed these studies thoroughly and determined that they do not support a causal link. The Panel stated that causation would depend on the migration of talc from the perineum to the ovaries. There is no conclusive explanation for the presence of talc in the ovaries reported in some studies. However, the Panel agreed that there is no known physiological mechanism by which talc can plausibly migrate from the perineum to the ovaries. Further, the Panel noted that if typical perineal applications of talc increased the risk of ovarian cancer, then it would be expected to increase the risks of uterine and, especially, cervical cancer as well; the absence of reports of associations between perineal talc use and either uterine or cervical cancer indicates that perineal talc application does not cause ovarian cancer. Additional support for this conclusion comes from, for example, studies demonstrating that the use of talc-dusted condoms or diaphragms, which would clearly result in exposure close to the cervical opening, was generally not associated with increased RR estimates for ovarian cancer.

Studies have also examined whether the inhalation of cosmetic-grade talc is associated with respiratory tract cancers. Although an inhalation study performed by the NTP using nonasbestiform, cosmetic-grade talc concluded that there was some evidence of carcinogenic activity in male rats and clear evidence in female rats, the Panel stated that these results were attributable to an artifactual effect caused by particle overload in the lungs of the rats. The talc that was used in this study, that is, micronized talc at high, saturating concentrations, had particle size distributions much smaller than those of cosmetic-grade talc. The Panel concluded that the use of talc at concentrations up to 35% in spray products, as reported for aerosol makeup bases, or even at 100% in powders, as reported for face powders, would not overwhelm pulmonary clearance mechanisms and would, therefore, not cause pulmonary overload or adverse respiratory effects attributable to cosmetic talc use.

One group of researchers looked at the effect of intratracheal administration of talc plus B[a]P in hamsters, concluding that talc may be co-carcinogenic when administered with B[a]P. The Expert Panel noted the potential for co-carcinogenicity but determined that the results of these studies were not attributable to a specific effect of talc, appropriate controls were not used, including control animals exposed to B[a]P alone and, thus, the results were not relevant for assessing the safety of the cosmetic use of talc.

Finally, the Panel warned that talc should not to be used on skin where the epidermal barrier is removed or on skin that has greater than first degree burns. Case reports were available in which granulomas formed if talc was applied to skin when the epidermal barrier was absent.

Conclusion

The CIR Expert Panel concluded that talc is safe in the present practices of use and concentration described in this safety assessment.

Author Contribution

M. Fiume contributed to conception and design; acquisition, analysis, and interpretation; and drafted the article. I. Boyer contributed to conception and design; acquisition, analysis, and interpretation; drafted the article, and critically revised the article. L. Gill, W. Bergfeld, D. Belsito, C. Klaassen, J. Marks, R. Shank, T. Slaga, and P. Snyder contributed to conception and design, analysis and interpretation, and critically revised the article. R. Hill and D. Liebler contributed to conception and design, analysis and interpretation, and critically revised the article. Former CIR Director F. Alan Anderson contributed to conception and design, analysis, and interpretation and critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

Authors' Note

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ARTICLE

Perineal Powder Use and Risk of Ovarian Cancer

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Background Case-control studies have reported an increased risk of ovarian cancer among talc users; however, the only cohort study to date found no association except for an increase in serous invasive ovarian cancers. The purpose of this analysis was to assess perineal powder use and risk of ovarian cancer prospectively in the Women's Health Initiative Observational Study cohort.

Methods Perineal powder use was assessed at baseline by self-report regarding application to genitals, sanitary napkins, or diaphragms and duration of use. The primary outcome was self-reported ovarian cancer centrally adjudicated by physicians. Cox proportional hazard regression was used to estimate risk, adjusting for covariates, including person-time until diagnosis of ovarian cancer (n = 429), death, loss to follow-up, or September 17, 2012. All statistical tests were two-sided.

Results Among 61 576 postmenopausal women, followed for a mean of 12.4 years without a history of cancer or bilateral oophorectomy, 52.6% reported ever using perineal powder. Ever use of perineal powder (hazard ratio [HR]$_{adj}$ = 1.06, 95% confidence interval [CI] = 0.87 to 1.28) was not associated with risk of ovarian cancer compared with never use. Individually, ever use of powder on the genitals (HR$_{adj}$ = 1.12, 95% CI = 0.92 to 1.36), sanitary napkins (HR$_{adj}$ = 0.95, 95% CI = 0.76 to 1.20), or diaphragms (HR$_{adj}$ = 0.92, 95% CI = 0.68 to 1.23) was not associated with risk of ovarian cancer compared with never use, nor were there associations with increasing durations of use. Estimates did not differ when stratified by age or tubal ligation status.

Conclusion Based on our results, perineal powder use does not appear to influence ovarian cancer risk.

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In 2013, it is estimated that there will be 22 240 new cases of ovarian cancer and 14 030 ovarian cancer deaths in the United States (US) alone (1). Since the 1960s, there has been speculation that the use of perineal powder is associated with ovarian cancer. In 2006, the International Agency for Research on Cancer (IARC) reviewed studies examining perineal powder use and ovarian cancer and classified talc as a possible carcinogen (2,3). The proportion of US women ever using talc powder on the perineum was estimated in 2001 to be approximately 40% (4), whereas 52% reported ever use of perineal powder in 1993–1998 within the Women's Health Initiative (WHI) (5).

The primary proposed mechanism linking perineal powder use to ovarian cancer is an inflammatory response (6). Talc particulates from perineal application have been shown to migrate to the ovaries (6), disrupting the surface ovarian epithelial tissue leading to entrapment of the talc particles within inclusion cysts (7). Furthermore, tubal ligation and/or hysterectomy, which would eliminate the pathway of talc particulates to the ovaries, are associated with reduced ovarian cancer risk (6).

A meta-analysis examining the risk of ovarian cancer among ever perineal powder users vs non-users showed odds ratios (ORs) of 1.40 (95% confidence interval [CI] = 1.29 to 1.52) for population-based case-control, 1.12 (95% CI = 0.92 to 1.36) for hospital based case-control, and 1.35 (95% CI = 1.26 to 1.46) for all case-control studies (2). More recently, a large pooled analysis found that ever use of perineal powder increased epithelial ovarian cancer risk by 24% compared with non-use (OR = 1.24, 95% CI = 1.15 to 1.33) (8). Increased risk was associated with invasive serous, endometrioid, clear cell, and borderline serous subtypes of epithelial ovarian cancer (8). However, when looking at the lifetime number of applications of perineal powder, there was no statistically significant trend for increasing applications, attributed to difficulty in recalling details of frequency and duration of perineal powder use (8).

To date there has only been one prospective study conducted examining perineal powder use and risk of ovarian cancer (9). In the Nurses' Health Study (NHS) cohort, no overall association was found between ever use of perineal powder and epithelial ovarian cancer (relative risk [RR] = 1.09, 95% CI = 0.86 to 1.37) or serous ovarian cancers (RR = 1.26, 95% CI = 0.94 to 1.69) (9). However, there was a 40% (95% CI = 1.02 to 1.91) increase in risk for serous

invasive ovarian cancer with ever perineal powder use, which comprises 86% of serous ovarian cancers in this cohort (9).

Limitations of recall bias and misclassification make it difficult to determine the true relationship between perineal powder (10), a commonly used cosmetic product, and ovarian cancer, a disease with poor survival and few known modifiable risk factors. The prior prospective cohort study, which should not be affected by recall bias, had no information on duration of use limiting interpretation. Here we expand on the available evidence by assessing perineal powder use and risk of ovarian cancer in the Women's Health Initiative Observational Study (WHI-OS). The WHI-OS is a large cohort that collected information on several application areas of perineal powder use and their respective durations of use.

Methods

Study Population

The WHI-OS enrolled 93 676 women from 40 clinical centers across the United States from 1993 to 1998 (11). Women were eligible if they were aged 50 to 79 at enrollment, postmenopausal, and planned to reside in the area for at least three years (11). Women were excluded from the WHI-OS if they were participating in another clinical trial, unlikely to survive three years due to medical conditions, or had conditions that would interfere with study participation (11). Participants completed annual mailed questionnaires to update information on risk factors and outcomes, including ovarian cancer (11). Written informed consent was obtained from participants, and all clinical centers were approved by their respective institutional review boards (11). The current analysis was approved by the University of Massachusetts, Amherst Human Subjects Review Committee.

For this analysis, participants were additionally excluded if they reported a bilateral oophorectomy or an unknown number of ovaries at baseline (n = 20 960), a history of any cancer at baseline except nonmelanoma skin cancer (n = 10 622), or were missing exposure or follow up information (n = 516). After applying the exclusion criteria, 61 576 participants with 429 adjudicated incident ovarian cancer cases remained.

Exposure Ascertainment

Perineal powder use was assessed via self-report at baseline. Participants were asked, "Have you ever used powder on your private parts (genital areas)?" Those who responded yes further indicated the duration of use with the following possible responses: less than 1 year, 1–4 years, 5–9 years, 10–19 years, or 20 or more years. For persons that reported ever use of a diaphragm, participants were asked, "Did you ever use powder on your diaphragm?" and those who responded yes further indicated duration. The third category evaluated was "Did you ever use powder on a sanitary napkin or pad?" with those responding yes also reporting duration. Each area of application variable was assessed dichotomously and the duration of use, collapsed into fewer categories because of small numbers, was assessed categorically as never, 9 years or less, or 10 or more years. A combined ever perineal powder variable and duration variable for any powder use was created; where ever use was defined as report of ever use of any of the three application categories, never was report of never use for all three categories, and duration was the maximum duration reported of any single area of application, because we could not exclude the possibility that applications were concurrent. Lastly, all possible combinations of the three application areas were assessed.

Outcome Ascertainment

Ovarian cancer cases were initially self-reported by participants in the WHI-OS on annual questionnaires. Medical records, including hospital discharge summaries and pathology reports, were requested for each self-reported case and adjudicated by a physician at the local Clinical Center and then centrally by the WHI's Clinical Coordinating Center (11).

Covariate Ascertainment

Potential covariates considered included age, race, education, alcohol servings per week, smoking status, metabolic equivalent (MET) hours per week of recreational physical activity, Body Mass Index (BMI), and self-reported family history of ovarian or breast cancer. Reproductive factors considered were age at menarche, age at menopause, age at first birth, age at last birth, parity, breastfeeding duration, history of tubal ligation, history of hysterectomy, history of irregular cycles, history of endometriosis, duration of oral contraceptive use, and duration of postmenopausal hormone use. All covariates were from baseline and were not updated.

Statistical Analysis

To estimate the association between perineal powder use and ovarian cancer, proportional hazard regression models were used. Participants contributed person-time until diagnosis of ovarian cancer, death, loss to follow-up, or September 17, 2012, whichever came first. Participants with other cancers were still considered at risk for ovarian cancer and were not censored at the time of other cancer diagnoses. Information on incident oophorectomy during follow-up was not available and thus participants were not censored in this analysis. The proportional hazards assumption was tested using weighted Schoenfeld residuals.

Covariates were included in the adjusted model according to purposeful selection, where covariates with Wald P values of .25 or less in age-adjusted models were entered into an initial multivariable model and then each covariate was subsequently tested individually via likelihood ratio tests in order of decreasing Wald P values. Variables that had P values of .10 or less during the backwards elimination were kept in the model until a parsimonious model was obtained. Additional variables shown in previous literature (8,9) but not statistically significant in our population were also included in the final multivariable model. Lastly, family history of breast cancer and personal history of endometriosis did not change estimates and were not included in the final multivariable model.

Models fitted included the following independent variables: 1) combined ever perineal powder use, 2) ever powder use by application area (ie, applied to genitals, applied to diaphragm, or applied to sanitary napkins), 3) duration of use by application area, and 4) application area combinations (ie, genital only, diaphragm only, sanitary napkin only, genital and sanitary napkin, genital and diaphragm, diaphragm and sanitary napkin, and all three areas of application). For duration models, test for trend was used to evaluate linear trends across duration categories by modeling the

categories as a continuous variable in the multivariable regression models.

Because powder particles may not reach the ovaries due to tubal ligation and because previous studies have shown a stronger association between powder use and ovarian cancer in women without tubal ligation (4), we separately examined women without tubal ligation. We also stratified by age at baseline, because older women may have had more potential for exposure to talc contaminated with asbestos. Additionally, associations by ovarian cancer histological subtype were evaluated. All analyses were performed using Stata v.12.1 (StataCorp, College Station, TX) and two-sided P values of .05 or less were considered statistically significant.

Results

The average age of the participants at baseline was 63.3 years. Participants were followed for a mean of 12.4 years; never powder users were followed for a mean of 12.2 years (range = 0.12 to 17.9 years) and ever powder users were followed for a mean of 12.6 years (range = 0.03 to 18.0). The majority of the participants were white (83.7%), had less than a college degree (56.1%), and were overweight/obese (57.2%). Approximately half (52.6%) of the population reported ever use of perineal powder. Ever powder users were heavier (27.5 kg/m^2 vs 26.5 kg/m^2, $P < .0001$) and were more likely to have used oral contraceptives (44% vs 36%, $P < .0001$) and/or diaphragms (50.8% vs 37.3 %, $P < .0001$) than never users (Table 1).

Use of powder on the genitals was associated with a 12% increase in the multivariable-adjusted hazard ratio of ovarian cancer (HR_{adj} = 1.12, 95% CI = 0.92 to 1.36), though this was not statistically significant (Table 2). Use of powder on sanitary napkins (HR_{adj} = 0.95, 95% CI = 0.76 to 1.20) or diaphragms (HR_{adj} = 0.92, 95% CI = 0.68 to 1.23) also was not associated with risk. Duration of powder use on the genitals, sanitary napkins, or on the diaphragm was not associated with ovarian cancer; P_{trend} for years of use: .67, .69, and .67 respectively. Combined ever powder use from any of the three application areas did not show an association with ovarian cancer risk (HR_{adj} = 1.06, 95% CI = 0.87 to 1.28). For combined duration of use, which was the longest duration of use among the three areas of application, there was no evidence of an association with risk of ovarian cancer [P_{trend} for years of use: .77]. Use of powder on genitals, the most common application area, for 20 or more years was not associated with increased risk of ovarian cancer compared with never users (HR_{adj} = 1.10, 95% CI = 0.82 to 1.48). In a sensitivity analysis, invasive serous ovarian cancer risk was not increased (HR_{adj} = 0.96, 95% CI = 0.65 to 1.41), even in women reporting durations of use greater than 10 years.

There was no evidence of an association between perineal powder use and ovarian cancer risk by category of application (Table 3). Combined ever powder use was not associated with individual subtypes of ovarian cancer (Table 4). The multivariable-adjusted hazard ratio for serous ovarian cancer was 1.16 (95% CI = 0.88 to 1.53). Additionally, duration of combined ever powder use was also not shown to be associated with any subtype of ovarian cancer (results not shown).

The associations of combined ever powder use and ovarian cancer did not statistically differ by tubal ligation status (results not shown). When stratified by age group at baseline, hazard estimates also did not statistically differ ($P_{interaction}$ = .37); HR_{adj} for younger than 50 to 59 years = 1.29, 95% CI = 0.91 to 1.82; HR_{adj} for those 60 to 69 years = 0.94, 95% CI = 0.70 to 1.26; and HR_{adj} for those 70 to 79 years = 1.01, 95% CI = 0.68 to 1.48. When restricted to only whites or to those who had never used oral contraceptives, results were again unchanged.

Table 1. Characteristics of postmenopausal women according to perineal powder use status (n = 61 285): Women's Health Initiative Observational Study, 1993–2012

Characteristic, n (%)	Never perineal powder use n = 29 066	Ever perineal powder use n = 32 219
Race		
White	24 006 (82.6)	27 336 (84.8)
Nonwhite	4991 (17.2)	4811 (14.9)
Body mass index category, kg/m^2		
<25.0	13 056 (44.9)	12 461 (38.7)
25.0–29.9	9734 (33.5)	10 799 (33.5)
30.0 +	5935 (20.4)	8571 (26.6)
Smoking status		
Never	15 347 (52.8)	15 621 (48.5)
Past	11 481 (39.5)	14 339 (44.5)
Current	1912 (6.6)	1881 (5.8)
Duration of oral contraceptive use, y		
Never	17 877 (61.5)	17 954 (55.7)
<5	6241 (21.5)	7858 (24.4)
5 to <10	2528 (8.7)	3270 (10.2)
10 to <15	1650 (5.7)	2125 (6.6)
15+	760 (2.6)	1005 (3.1)
Diaphragm use	10 826 (37.3)	16 353 (50.8)
Tubal ligation	4929 (17.0)	5901 (18.3)
Hysterectomy	6878 (23.7)	8285 (25.7)
Family history of ovarian cancer	606 (2.1)	660 (2.1)
Parity		
0	3687 (12.7)	3769 (11.7)
1–2	9773 (33.6)	11 585 (36.0)
3–4	11 101 (38.2)	12 609 (39.1)
5+	4365 (15.0)	4098 (12.7)
Age at last birth, y		
Never had term pregnancy	6219 (21.4)	6260 (19.4)
< 20	210 (0.7)	324 (1.0)
20–29	9143 (31.5)	11480 (35.6)
30+	13 011 (44.8)	13 668 (42.4)
Duration of postmenopausal hormone use, y		
Never	13 381 (46.0)	13 880 (43.1)
<5	6498 (22.4)	7546 (23.4)
5 to <10	3783 (13.0)	4567 (14.2)
10 to <15	2688 (9.3)	3128 (9.7)
15+	2716 (9.3)	3097 (9.6)

Discussion

In this large prospective study, ever perineal powder use was not associated with ovarian cancer risk, nor was it associated with ovarian cancer when assessed by area of application, duration of use, or ovarian cancer subtype. While many case-control studies have shown an approximately 24–40% increase in risk of ovarian cancer (2,8) for powder users, we did not find evidence of this association in our large, prospective analysis.

The meta-analysis of 20 case-control studies by Langseth and colleagues found a 35% increase in the odds of epithelial ovarian

Table 2. Age and multivariable-adjusted hazard ratios of ovarian cancer by area of perineal powder application (n = 61 576): Women's Health Initiative Observational Study, 1993–2012

Variable	No. of cases	Person-years	Age-adjusted HR (95% CI)	P_{trend} †	Multivariable HR* (95% CI)	P_{trend} †
Powder use on genitals						
Never	247	457 855	1.0 (referent)	.63	1.0 (referent)	.67
Ever‡	181	304 867	1.13 (0.93 to 1.37)		1.12 (0.92 to 1.36)	
Less than 9 years	112	173 118	1.24 (0.99 to 1.55)		1.23 (0.98 to 1.54)	
10 or more years	68	129 647	0.98 (0.75 to 1.29)		0.98 (0.75 to 1.29)	
Powder use on sanitary napkins						
Never	336	590 351	1.0 (referent)	.70	1.0 (referent)	.69
Ever‡	93	172 712	0.96 (0.76 to 1.21)		0.95 (0.76 to 1.20)	
Less than 9 years	62	114 305	0.98 (0.75 to 1.28)		0.96 (0.73 to 1.26)	
10 or more years	30	56 174	0.93 (0.64 to 1.35)		0.95 (0.65 to 1.37)	
Powder use on diaphragm						
Never	373	661 239	1.0 (referent)	.78	1.0 (referent)	.67
Ever‡	52	97 714	0.94 (0.70 to 1.25)		0.92 (0.68 to 1.23)	
Less than 9 years	35	67 468	0.93 (0.66 to 1.32)		0.91 (0.64 to 1.30)	
10 or more years	17	29 202	0.99 (0.61 to 1.60)		0.95 (0.58 to 1.56)	
Combined ever powder use§						
Never	197	361 583	1.0 (referent)	.67	1.0 (referent)	.77
Ever‡	232	404 983	1.07 (0.89 to 1.30)		1.06 (0.87 to 1.28)	
Less than 9 years	135	228 931	1.12 (0.90 to 1.39)		1.09 (0.88 to 1.36)	
10 or more years	97	173 307	1.03 (0.81 to 1.31)		1.02 (0.80 to 1.30)	

* Adjusted for: Age (continuous), race (white, nonwhite, missing), oral contraceptive duration in years (never, <5, 5 to <10, 10 to <15, 15+, missing), hormone replacement therapy duration in years (never, <5, 5 to <10, 10 to <15, 15+, missing), family history (yes, no, missing), age (y) at last birth (never, <20, 20 to <30, 30+, missing), body mass index in kg/m² (<25.0, 25.0 to <30.0, 30.0+, missing), smoking (never, past, current, missing), tubal ligation (yes, no, missing), and parity (0, 1 to 2, 3 to 4, 5+, children, missing).

† Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated in cox proportional hazard regression models; P_{trend} was estimated by modeling categories as continuous. All statistical tests were two-sided.

‡ Person-years may not add up; duration information was missing for some.

§ Combined ever powder use is the longest duration of use among the applications to genitals, sanitary napkins, and diaphragms.

Table 3. Age and multivariable-adjusted hazard ratios for ovarian cancer by combined categories of powder use (n = 61 576): Women's Health Initiative Observational Study, 1993–2012

Variable	No. of cases	Person-years	Age-adjusted HR* (95% CI)	Multivariable HR* (95% CI)
Powder Type Used				
No powder	193	355 523	1.0 (referent)	1.0 (referent)
Only genital powder	96	158 130	1.14 (0.90 to 1.46)	1.13 (0.88 to 1.45)
Only diaphragm powder	19	42 367	0.82 (0.51 to 1.32)	0.80 (0.50 to 1.29)
Only sanitary napkin powder	28	50 051	1.04 (0.70 to 1.54)	1.01 (0.68 to 1.50)
Genital and sanitary napkin powder	55	96 173	1.09 (0.80 to 1.47)	1.08 (0.80 to 1.46)
Genital and diaphragm powder	24	29 858	1.49 (0.98 to 2.28)	1.45 (0.95 to 2.23)
Diaphragm and sanitary napkin powder	4	6858	1.06 (0.40 to 2.86)	1.02 (0.38 to 2.74)
Genital, diaphragm, and sanitary napkin powder	5	18 331	0.51 (0.21 to 1.24)	0.50 (0.21 to 1.22)

* Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated in cox proportional hazard regression models. All statistical tests were two-sided. Multivariable HR adjusted for: age (continuous), race (white, nonwhite, missing), oral contraceptive duration in years (never, <5, 5 to <10, 10 to <15, 15+, missing), hormone replacement therapy duration in years (never, <5, 5 to <10, 10 to <15, 15+, missing), family history (yes, no, missing), age (y) at last birth (never, <20, 20 to <30, 30+, missing), body mass index in kg/m² (<25.0, 25.0 to <30.0, 30.0+, missing), smoking (never, past, current, missing), tubal ligation (yes, no, missing), and parity (0, 1 to 2, 3 to 4, 5+, children missing).

cancer among ever perineal powder users compared to never-users (2), and the pooled analysis of eight case-control studies by Terry and colleagues found a 24% increase in the same group (8). Langseth and colleagues did not assess dose-response or risk among subtypes of ovarian cancer (2). Terry and colleagues assessed lifetime applications of perineal powder and found no statistically significant trend with increasing lifetime applications (8). This corroborates our results that there was no statistically significant risk with increasing duration of perineal powder use, though they were able to capture both frequency and duration (8), whereas we only had duration. Terry and colleagues found elevated risks for invasive serous, borderline serous, endometrioid, and clear cell subtypes of ovarian cancer (8), which we did not observe. One potential reason that case-control studies have found slight increases in risk is the potential for an overestimation of the true association due to recall bias, because the participants are aware of their ovarian cancer status when reporting powder

Table 4. Age and multivariable-adjusted hazard ratios for combined ever powder use by subtype of ovarian cancer (n = 61 576): Women's Health Initiative Observational Study, 1993–2012

Variable	No. of cases	Person-years	Age-adjusted HR* (95% CI)	Multivariable HR* (95% CI)
Serous†				
Never	87	355 523	1.0 (referent)	1.0 (referent)
Ever	117	404 983	1.18 (0.89 to 1.56)	1.16 (0.88 to 1.53)
Serous Invasive				
Never	80	355 523	1.0 (referent)	1.0 (referent)
Ever	105	404 983	1.16 (0.87 to 1.55)	1.13 (0.84 to 1.51)
Mucinous				
Never	12	355 523	1.0 (referent)	1.0 (referent)
Ever	13	404 983	0.98 (0.44 to 2.14)	1.03 (0.47 to 2.27)
Endometrioid				
Never	13	355 523	1.0 (referent)	1.0 (referent)
Ever	20	404 983	1.39 (0.69 to 2.79)	1.29 (0.64 to 2.61)
Other				
Never	47	355 523	1.0 (referent)	1.0 (referent)
Ever	54	404 983	1.04 (0.71 to 1.54)	1.04 (0.70 to 1.54)

* Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated in cox proportional hazard regression models. All statistical tests were two-sided. Multivariable HR adjusted for: age (continuous), race (white, nonwhite, missing), oral contraceptive duration in years (never, <5, 5 to <10, 10 to <15, 15+, missing), hormone replacement therapy duration in years (never, <5, 5 to <10, 10 to <15, 15+, missing), family history (yes, no, missing), age (y) at last birth (never, <20, 20 to <30, 30+, missing), body mass index in kg/m^2 (<25.0, 25.0 to <30.0, 30.0+, missing), smoking (never, past, current, missing), tubal ligation (yes, no, missing), and parity (0, 1 to 2, 3 to 4, 5+, children missing).

† Includes borderline cancers.

exposure. The prospective nature of our study would eliminate the potential for recall bias. Additionally, the case-control studies tended to have a younger population than our study, which included both premenopausal and postmenopausal ovarian cancers (2,8), whereas the WHI cohort consisted only of postmenopausal ovarian cancers. Ovarian cancer that occurs prior to menopause may have a different etiology than ovarian cancer occurring afterwards.

We found similar results to that of the NHS, the only other prospective cohort, which had a similar sample size and number of ovarian cancer cases to our study. Ever use of perineal powder did not appear to be associated with ovarian cancer in the NHS (9), similar to our findings. The results of Gertig and colleagues were also null for use on the genitals and for use on sanitary napkins (9). Additionally, neither our study nor the NHS found associations with serous ovarian cancer, endometrioid, or mucinous ovarian cancers, although subgroup sample size may have reduced statistical power to test these associations. In contrast to our results, the study by Gertig and colleagues found a 40% increase in invasive serous ovarian cancer among ever powder users compared with never powder users (9).

Strengths of our study included large sample size with a substantial number of ovarian cancer cases, a prospective cohort design, good case ascertainment, and detailed information on most ovarian cancer risk factors. We also had information on duration of powder use, qualifiers not available in several earlier studies, including the previous cohort study (2,8,9).

One potential limitation of our analyses includes a lack of information regarding oophorectomy after baseline, which would result in the inclusion of some women not at risk for ovarian cancer in the analytical cohort. However, the impact was likely to be minor, as a previous study in the WHI-OS had reported the number of persons with incident bilateral oophorectomies to be less than 250 (out of more than 90 000 participants) during nearly eight years of follow-up (12). While the prospective nature of the study design eliminates recall bias, it does not eliminate potential for nondifferential misclassification of the exposure. Women still needed to recall past perineal powder use and duration and thus may have trouble recollecting specifics regarding the use of perineal powder, leading to a bias toward the null. Information regarding powder use was not collected after baseline, and there is potential for never users to begin using powder; however, this is unlikely because the women are postmenopausal, reducing need to use perineal powder on diaphragms or sanitary napkins. We also had no specific data regarding the frequency of powder use in our sample. Frequency of use, as well as duration may influence ovarian cancer risk. We may have been comparing long-term infrequent users with short-term frequent users. If we had frequency of use in addition to the duration, we could have looked at intensity of use, which may be more accurate, and shown a dose response relationship. However, Terry and colleagues did not find a dose response relationship either when taking into account frequency and duration (8).

When restricted to women without tubal ligation status, the estimates for the association between combined ever perineal powder use and ovarian cancer were not increased. While some studies have found stronger associations between powder use and ovarian cancer in women that have not undergone a tubal ligation (4), the results from our study did not support this previous finding. The pooled analysis (8) and the NHS cohort (9) also did not find evidence of stronger associations in women without tubal ligations.

While we had information on duration of use, it is unknown during which years the perineal powder was used. Talc powder had potential for asbestos contamination (13) until 1976, when the Cosmetic, Toiletry, and Fragrance Association required all cosmetic talc products to be free of asbestos (14). Therefore, those using powder prior to 1976 may have been potentially exposed to asbestos, a known carcinogen. The pooled analysis and meta-analysis also included case-control studies not within the United States

(2,8), which potentially have different regulations regarding perineal powder and earlier studies that may have been more likely to include exposure to contaminated perineal powder (2). However, risk estimates in more recent studies are similar to earlier studies (2), reducing the likelihood that confounding by asbestos is driving the findings. Additionally, assuming older women in the cohort could have been exposed longer to perineal powder with potential contamination compared with younger women, we did not see statistically significant differences in risk when stratified by age group, further suggesting asbestos contamination is not a likely explanation.

The WHI-OS queried general perineal powder use rather than talc powder use, and we had no specific information regarding the content of talc in products used, which the previous literature reviewed by IARC suggested to be the possible carcinogen of concern (2). However, the NHS cohort and most studies included within the pooled analyses asked about general perineal powder use as well (2,8,9). In summary, perineal powder use did not appear to be associated with ovarian cancer risk in this large sample of postmenopausal women, even with use for long durations.

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Original Contribution

Risk Factors for Epithelial Ovarian Cancer by Histologic Subtype

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Previous epidemiologic studies suggest that the major histologic subtypes of epithelial ovarian cancer may have different risk factor profiles; however, no known prospective study has systematically examined differences in risk by subtype. The authors used Cox proportional hazards regression, stratified by histologic subtype and time period, to examine the association between ovarian cancer risk factors and incidence of serous invasive, endometrioid, and mucinous ovarian cancers in the US Nurses' Health Study (1976–2006) and Nurses' Health Study II (1989–2005). For each exposure, they calculated *P*-heterogeneity using a likelihood ratio test comparing models with separate estimates for the 3 subtypes versus a single estimate across subtypes. Analysis included 221,866 women and 721 cases with the histologies of interest (496 serous invasive, 139 endometrioid, 86 mucinous). In analyses of reproductive/hormonal exposures, the associations with age, duration of breastfeeding, age at natural menopause, and duration of estrogen use differed significantly by subtype (all *P*-heterogeneity $\leq$0.05). The associations with several nonreproductive exposures also appeared to vary by subtype, but only the association with smoking differed significantly (*P*-heterogeneity = 0.03). Results suggest that associations with several ovarian cancer risk factors vary by subtype, and these differences are consistent with known similarities between each major histologic subtype and its normal tissue counterpart.

adenocarcinoma, mucinous; carcinoma, endometrioid; cystadenocarcinoma, serous; histology; ovarian neoplasms

Abbreviations: AUC, area under the receiver operating characteristic curve; CI, confidence interval; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; RR, incidence rate ratio.

Epithelial ovarian cancers often are analyzed as a single outcome in epidemiologic studies, despite evidence of differences in their natural history, morphology, and gene/protein expression (1–4). The most common histologic subtypes of epithelial ovarian cancer each resemble a different normal tissue in morphology and gene expression (4, 5), and previous studies suggest their etiology may differ as well. In a pooled analysis of 10 case-control studies, oral contraceptive use and parity were inversely associated with all subtypes, whereas associations with nonreproductive exposures, particularly body mass index and smoking, differed by subtype (6). Other studies have reported differences in associations with both reproductive and nonreproductive exposures for mucinous versus nonmucinous cancers (7–12).

Although these studies suggest that some associations differ by subtype, the data are inconsistent (6–10, 13, 14), and no known comprehensive, prospective analysis of differences in risk factors by histologic subtype has been published. In addition, most prior studies analyzed each subtype separately and did not report a statistical test comparing results across subtypes. We therefore used polytomous regression models to examine the association between known and suspected risk factors for ovarian cancer and incidence of the serous invasive, endometrioid, and mucinous subtypes in the Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII).

MATERIALS AND METHODS

Study population

The NHS was established in 1976 and the NHSII in 1989 among 121,700 US female registered nurses aged 30–55 years and 116,430 US female registered nurses aged 25–42 years, respectively. Participants completed an initial questionnaire and biennial follow-up questionnaires,

providing information on lifestyle factors and disease diagnoses. Follow-up is high in both cohorts; we obtained 95.2% of the total possible person-years through June 2006 in the NHS and 93.6% through June 2005 in the NHSII. The Committee on the Use of Human Subjects in Research at Brigham and Women's Hospital, Boston, Massachusetts, approved both studies.

Exposure data

We obtained information on exposures of interest from the biennial questionnaires. At baseline, participants reported their birth date, age at menarche, and height. We requested information on parity, oral contraceptive use, tubal ligation, hysterectomy/oophorectomy, menopausal status, age at menopause, postmenopausal hormone use, weight, physical activity, smoking status, and family history of breast/ovarian cancer on multiple questionnaires during follow-up. In our analysis, we updated values for these covariates when new data were available and otherwise carried forward values from the previous cycle. We requested data on total duration of breastfeeding across all pregnancies in 1986 (NHS) and 1993 (NHSII) and on duration of breastfeeding for each child in 1997 (NHSII only). Information on frequency of genital talc use was collected in 1982 (NHS only).

Identification of ovarian cancer cases

We collected information on new ovarian cancer diagnoses on each questionnaire. For all reported cases, as well as deaths due to ovarian cancer identified through family members, the National Death Index (15, 16), or the US Postal Service, we obtained medical records related to the diagnosis. A gynecologic pathologist (J. H.) blinded to exposure status reviewed the medical records to confirm the diagnosis, stage, histologic type/subtype, and invasiveness (17). Our analysis included cases of epithelial ovarian cancer ($n = 885$) and primary peritoneal cancer ($n = 39$) confirmed by pathology report review and diagnosed between baseline and June 2006 (NHS) or 2005 (NHSII).

Statistical analysis

Participants accrued person-time from the return date of the baseline questionnaire until the date of ovarian cancer diagnosis, diagnosis of any other cancer (excluding nonmelanoma skin cancer), bilateral oophorectomy, pelvic irradiation, death, or the end of follow-up. At baseline, we excluded women with bilateral oophorectomy (NHS: $n = 7,669$; NHSII: $n = 2,229$), menopause due to pelvic irradiation (NHS: $n = 99$; NHSII: $n = 30$), or cancer other than nonmelanoma skin cancer (NHS: $n = 3,314$; NHSII: $n = 1,050$). In addition, we excluded women with missing data on any exposure of interest except breastfeeding duration, talc use, and family history of ovarian cancer, which were not collected at baseline, and age at natural menopause, which was missing for women with a hysterectomy before menopause. We included missing indicators for these 4 exposures in our models to avoid excluding too many women from the analysis. Participants contributed person-time only for follow-up periods for which data were complete. Furthermore, we excluded person-time ($\leq$0.3% of the total) when any continuous variable had an outlying value, using the generalized extreme studentized deviate many-outlier detection approach (18).

In analyses of reproductive/hormonal exposures, we modeled age, parity among parous women, duration of breastfeeding, duration of oral contraceptive use, age at natural menopause, and duration of postmenopausal use of unopposed estrogens as continuous variables to minimize the number of parameters in the model. We used binary variables to model menopausal status (postmenopause vs. premenopause/perimenopause), cohort (NHS vs. NHSII), and parity, tubal ligation, and hysterectomy without bilateral oophorectomy (yes/no). Because of evidence of a nonlinear association with age, we used a spline with a single knot at age 50 years to estimate linear associations with age separately for women younger than age 50 years versus 50 years of age or older.

In an alternative analysis, we modeled ovulatory years and duration of menopause instead of age, parity, duration of oral contraceptive use, and age at natural menopause. We calculated ovulatory years as current age (if premenopausal) or age at natural menopause minus age at menarche, years of oral contraceptive use, and parity (1 year per pregnancy), and we included a separate variable for total duration of breastfeeding. We calculated duration of menopause as current age minus age at natural menopause for postmenopausal women, and we coded premenopausal/perimenopausal women as 0. For women with an unknown age at natural menopause because of hysterectomy before menopause, we excluded person-time after hysterectomy.

For the nonreproductive exposures, we modeled body mass index (weight (kg)/height (m)^2) and physical activity (cumulative average metabolic equivalent task-hours/week) continuously, regular genital talc use ($\geq$once/week vs. $<$once/week) and family history of breast/ovarian cancer (yes/no) as binary variables, and smoking status as 2 indicator variables for past or current (vs. never) smoking. Metabolic equivalent task-hours captures both duration and intensity of activity (3 metabolic equivalent task-hours is equivalent to walking 2–2.9 mph for 1 hour (1 mile = 1.6 km)), and cumulative average levels better reflect long-term activity and minimize within-person variation. In the NHS, data on metabolic equivalent task-hours were not available until 1986; we therefore assigned all participants 0 activity from 1976 to 1986 and secondarily evaluated the association with physical activity with follow-up beginning in 1986.

We used Cox proportional hazards regression, stratified by time period, to model the incidence rate ratio and 95% confidence interval of epithelial ovarian cancer for each exposure in the NHS and NHSII combined. We then restricted the analysis to cases with serous invasive/poorly differentiated, endometrioid, or mucinous histology and used Cox proportional hazards regression, stratified by type of outcome and time period, to allow for different associations by histologic subtype (19). We used data augmentation, such that each participant had a separate observation for each subtype. We coded the event variable as 1 (failed) if

the participant was diagnosed with the histologic subtype corresponding to that data row and as 0 otherwise; cases were censored for other subtypes at the time of diagnosis.

We compared a model that assumed different associations for all exposures by histologic subtype (full model) with a model with a single estimate across subtypes for one exposure at a time (reduced model). We calculated the *P*-heterogeneity using a likelihood ratio test, with the degrees of freedom equal to the difference between the numbers of parameters in the 2 models. Using a stepwise-down approach, we set exposures with a nonsignificant *P*-heterogeneity to have a single estimate across subtypes, so that the final model estimated 3 separate associations for exposures that differed significantly by subtype and a single estimate for all other exposures. All *P* values were 2-sided and were considered statistically significant if ≤ 0.05.

We evaluated goodness of fit by calculating the area under the receiver operating characteristic curve (AUC) for all cancers and stratified by subtype. For each observation, we determined a risk score using parameter estimates from the model, and we used the risk scores to calculate the Wilcoxon rank sum test statistic W by 5-year age group t. We calculated the Mann-Whitney $U_t = W_t - \frac{m_t(m_t+1)}{2}$ and $\hat{\theta}_t = \frac{U_t}{m_t n_t}$, where $\hat{\theta}_t$ is the probability that a random case has a higher risk score than a random control within age group t. We calculated the variance of $\hat{\theta}_t$ under the alternative hypothesis (20), and we calculated the overall AUC as the weighted average of $\hat{\theta}_t$ across t with weights $= 1/\mathrm{var}(\hat{\theta}_t)$.

We did not have adequate power to examine associations with clear-cell cancers separately because of the small number of cases ($n = 48$). However, we evaluated differences between serous versus nonserous (endometrioid/mucinous/clear-cell) and mucinous versus nonmucinous (serous/endometrioid/clear-cell) cancers. In secondary analyses, we examined differences between all 4 subtypes for the reproductive exposures only.

RESULTS

Our analysis included 221,866 women with 924 incident cases of confirmed epithelial ovarian cancer (NHS: 108,870 women and 797 cases; NHSII: 112,996 women and 127 cases). Of the cases of cancer, 496 were serous invasive (54%), 139 were endometrioid (15%), and 86 were mucinous (9%). The remaining 203 cases of cancer included 48 clear cell (5% of total), 71 noninvasive serous (8%), 21 carcinosarcoma (2%), 17 mixed (2%), and 46 other/unknown (5%).

In general, baseline characteristics of cases versus noncases were similar to those expected based on previous studies of known risk factors (Table 1). NHSII participants were younger than NHS participants and were more likely to have used oral contraceptives or have had a tubal ligation, were less likely to be parous or to smoke, were more physically active, and had lower mean parity but a longer mean duration of breastfeeding among parous women.

When we compared baseline characteristics of women subsequently diagnosed with a serous invasive, endometrioid, or mucinous tumor (Table 1), we found that serous invasive cases were slightly older, had higher parity, and were more physically active than endometrioid/mucinous cases. Endometrioid cases had a longer mean duration of estrogen use (NHS only) and a higher mean body mass index (NHSII only), were less likely to be parous (NHS only) or to have smoked, and were more likely to have a family history of breast cancer. Mucinous cases had a shorter mean duration of estrogen use (NHS only) and breastfeeding and were less physically active, less likely to have had a hysterectomy, and were more likely to have regularly used talc or to currently smoke (NHS only).

The associations with age (*P*-heterogeneity <0.001), duration of breastfeeding (*P*-heterogeneity = 0.03), age at natural menopause (*P*-heterogeneity = 0.05), and duration of estrogen use (*P*-heterogeneity = 0.009) differed significantly by subtype, whereas other exposures (e.g., oral contraceptive use) exhibited similar associations across the 3 subtypes (Table 2). Age among women less than 50 years was more strongly associated with serous invasive (incidence rate ratio (RR) = 1.15 per year, 95% confidence interval (CI): 1.10, 1.19) and endometrioid (RR = 1.12 per year, 95% CI: 1.06, 1.17) tumors than mucinous tumors. Among women aged 50 years or older, age was associated with a modest increase in risk of serous invasive cancers, was associated with a modest decrease in risk of endometrioid tumors, and was unassociated with mucinous cancers. Duration of breastfeeding was inversely associated with all 3 subtypes, but the association was strongest for mucinous tumors (RR = 0.43 per year). Age at natural menopause was positively associated with the endometrioid subtype only (RR = 1.13 per year, 95% CI: 1.04, 1.22). Duration of estrogen use was associated with a strong increase in risk of endometrioid cancers (RR = 1.87 per 5-year increase, 95% CI: 1.52, 2.31) and a weaker increase in risk of the other subtypes.

Although not statistically significant, there was some evidence of heterogeneity by subtype for parity, tubal ligation, and hysterectomy; the inverse association for oral contraceptive use was similar across subtypes. A first birth was associated with a borderline significant decrease in risk of serous invasive and endometrioid cancers but was unassociated with mucinous tumors. Each additional birth significantly decreased risk of the endometrioid subtype only (RR = 0.85, 95% CI: 0.74, 0.99). In general, tubal ligation and hysterectomy were more strongly inversely associated with endometrioid and mucinous cancers.

In an alternative reproductive model with ovulatory years and duration of menopause, associations with number of ovulatory years (*P*-heterogeneity = 0.04), duration of menopause (*P*-heterogeneity <0.001), and duration of breastfeeding (*P*-heterogeneity = 0.03) differed significantly by subtype (Table 3). Each 1-year increase in the number of ovulatory years was associated with a significant 8% increase in risk of serous invasive and endometrioid tumors but only a 3% increase in risk of mucinous tumors.

Building on the final reproductive model, the associations with several nonreproductive exposures appeared to differ by subtype, but only smoking differed significantly (*P*-heterogeneity = 0.03) (Table 4). Past smoking was associated with decreased risk of endometrioid tumors (RR = 0.59, 95% CI: 0.39, 0.90), whereas past/current smoking

Table 1. Baseline Characteristics of Epithelial Ovarian Cancer Cases and Noncases Among 108,870 Women in the NHS in 1976 and 112,996 Women in the NHSII in 1989

	NHS					NHSII				
	Noncases (n = 108,073)	All Epithelial (n = 797)	Serous Invasive (n = 451)	Endometrioid (n = 115)	Mucinous[a] (n = 69)	Noncases (n = 112,869)	All Epithelial (n = 127)	Serous Invasive (n = 45)	Endometrioid (n = 24)	Mucinous[a] (n = 17)
Reproductive/hormonal characteristics										
Mean										
Age, years	42	45	45	44	44	35	37	38	36	35
Duration of oral contraceptive use, months[b]	47	44	44	36	38	53	49	39	62	57
Duration of estrogen use, months[b]	34	44	43	75	20	15	0	0	0	0
Parity among parous women, no.	3.1	3.0	3.2	2.9	2.9	2.1	2.0	2.2	1.8	1.8
Duration of breastfeeding, months[c]	6	4	4	4	2	13	8	11	10	7
Ovulatory years, no.[d]	24	27	28	27	27	17	20	21	18	17
Percentage of the population										
Ever used oral contraceptives	48	38	35	38	43	83	85	87	83	82
Parous	94	90	91	82	95	70	63	67	67	53
Tubal ligation	13	8	9	7	10	16	13	18	4	6
Hysterectomy	13	14	18	10	6	4	6	7	8	0
Other characteristics										
Mean										
Body mass index, kg/m^2	24	24	24	24	23	24	26	24	29	24
Physical activity, MET-hours/week[e]	13	14	15	13	9	21	22	25	18	17
Percentage of the population										
Genital talc use >once/week[f]	28	29	29	30	40					
Past smoker	23	27	29	17	26	21	22	23	8	20
Current smoker	33	31	29	33	44	13	12	16	8	13
Family history of breast cancer	6	8	7	12	8	6	13	20	21	7
Family history of ovarian cancer[g]	3	5	6	0	19	2	1	4	0	0

Abbreviations: MET, metabolic equivalent task; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II.
[a] Includes borderline and invasive tumors.
[b] Among ever users of oral contraceptives or postmenopausal unopposed estrogens; in the NHSII, only 32 women had used unopposed estrogens at baseline.
[c] Total duration among parous women in 1986 for the NHS and 1993 for the NHSII.
[d] Current age (if premenopausal) or age at natural menopause minus (age at menarche + duration of oral contraceptive use in years + parity).
[e] Physical activity from 1986 for the NHS and 1989 for the NHSII; 3 MET-hours is equivalent to walking at an average pace of 2.0–2.9 miles/hour for 1 hour (1 mile = 1.6 km).
[f] Use among NHS participants only; collected in 1982.
[g] First collected in 1992 in the NHS and 1993 in the NHSII.

Table 2. Association Between Reproductive/Hormonal Exposures and Risk of Epithelial Ovarian Cancer, by Histologic Subtype, Among 108,870 Women in the NHS From 1976 to 2006 and 112,996 Women in the NHSII From 1989 to 2005[a]

	All Epithelial (*n* = 924)		Serous Invasive (*n* = 496)		Endometrioid (*n* = 139)		Mucinous (*n* = 86)[b]		*P*-Heterogeneity[c]
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	
Age among women <50 years, (per 1-year increase)[d]	1.11	1.09, 1.14	1.15	1.10, 1.19	1.12	1.06, 1.17	1.06	1.00, 1.12	<0.001
Age among women ≥50 years, (per 1-year increase)[e]	1.02	1.01, 1.04	1.04	1.02, 1.06	0.97	0.94, 1.00	1.00	0.96, 1.04	
Parous[f]	0.71	0.57, 0.89	0.73	0.53, 1.02	0.61	0.37, 1.03	1.17	0.56, 2.47	0.09
Parity among parous women[f]	0.94	0.89, 0.99	1.00	0.94, 1.06	0.85	0.74, 0.99	0.95	0.81, 1.13	
Breastfeeding (per 1-year increase)[g]	0.82	0.74, 0.91	0.84	0.73, 0.96	0.74	0.55, 1.00	0.43	0.25, 0.74	0.03
Oral contraceptive use (per 5-year increase)	0.84	0.75, 0.93	0.78	0.66, 0.91	0.77	0.58, 1.02	0.84	0.60, 1.17	0.91
Tubal ligation	0.68	0.56, 0.84	0.83	0.63, 1.09	0.59	0.34, 1.02	0.50	0.25, 1.01	0.26
Hysterectomy	0.69	0.52, 0.91	0.86	0.61, 1.20	0.68	0.39, 1.17	0.45	0.20, 0.98	0.20
Age at natural menopause (per 1-year increase)	1.03	1.00, 1.05	1.02	0.99, 1.06	1.13	1.04, 1.22	1.01	0.93, 1.10	0.05
Estrogen use (per 5-year increase)[h]	1.37	1.25, 1.50	1.28	1.14, 1.44	1.87	1.52, 2.31	1.31	0.89, 1.93	0.009

Abbreviations: CI, confidence interval; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; RR, incidence rate ratio.

[a] Estimates were adjusted for all variables in the table, plus cohort (NHS or NHSII), menopausal status (postmenopause vs. premenopause/perimenopause), missing data on breastfeeding duration (yes/no) because of noncompletion of questionnaire, and missing age at natural menopause (yes/no) because of hysterectomy prior to menopause.

[b] Includes borderline and invasive tumors.

[c] *P* value from likelihood ratio test comparing, for each covariate, the model with separate estimates for the serous invasive, endometrioid, and mucinous histologic subtypes with the model with a single estimate across the 3 subtypes.

[d] RR for each 1-year increase in age prior to age 50 years.

[e] RR for each 1-year increase in age at age 50 years or older.

[f] Parous: RR for 1 versus 0 children; parity among parous women: RR for each additional child after the first.

[g] Breastfeeding duration first collected in 1986 in the NHS and 1993 in the NHSII.

[h] Duration of postmenopausal use of unopposed estrogens.

was associated with a nonsignificant increased risk of mucinous cancers. Body mass index was positively associated with the endometrioid subtype (RR = 1.18 per 5 kg/m^2, 95% CI: 1.02, 1.38) but was unassociated with the other subtypes (*P*-heterogeneity = 0.06). There also were nonsignificant positive associations between physical activity and serous invasive cancers and between talc use and mucinous tumors. The results for physical activity were unchanged when 1986 was used as the baseline (results not shown).

For the association with all epithelial cancers, the AUC for the reproductive model (AUC = 0.624) was slightly higher than that for the ovulatory years model (AUC = 0.617), indicating that these models have similar discriminatory ability (Table 5). The goodness of fit for the reproductive model was highest for the endometrioid subtype (AUC = 0.714), intermediate for the mucinous subtype (AUC = 0.678), and lowest for the serous invasive subtype (AUC = 0.614). Adding the nonreproductive exposures improved the goodness of fit overall and for each subtype. Although the AUC for each model was based on a slightly different study population, the results were similar when we used the same population for all models (results not shown).

All results were essentially unchanged when we restricted analyses to the NHS only or excluded primary peritoneal cases (results not shown). In analyses of serous versus nonserous cancers, there were significant differences for the associations with age, parity, tubal ligation, and duration of breastfeeding but no differences for nonreproductive exposures (results not shown). When mucinous cancers were compared with nonmucinous cancers, the associations with only age, duration of breastfeeding, and number of ovulatory years differed significantly (results not shown). When we included clear-cell cancers in the reproductive model, the associations with age, parity, duration of estrogen use, and duration of breastfeeding differed significantly across the 4 subtypes (results not shown).

DISCUSSION

These results suggest that associations with several ovarian cancer risk factors differ by histologic subtype. We observed significant heterogeneity across the serous invasive, endometrioid, and mucinous subtypes for associations with both reproductive and nonreproductive exposures, including age, duration of breastfeeding, duration of estrogen use, and smoking status. There was some evidence of heterogeneity by subtype for several other exposures, including parity and

Table 3. Association Between Ovulatory Years and Other Reproductive/Hormonal Exposures and Risk of Epithelial Ovarian Cancer, by Histologic Subtype, Among 107,352 Women in the NHS From 1976 to 2006 and 112,632 Women in the NHSII From 1989 to 2005[a,b]

	All Epithelial (n = 767)		Serous Invasive (n = 397)		Endometrioid (n = 118)		Mucinous[c] (n = 80)		P-Heterogeneity[d]
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	
Ovulatory years (per 1-year increase)[e]	1.07	1.05, 1.08	1.08	1.06, 1.10	1.08	1.05, 1.11	1.03	1.00, 1.07	0.04
Duration of menopause (per 1-year increase)	1.02	1.01, 1.04	1.04	1.02, 1.06	0.96	0.93, 0.99	1.00	0.97, 1.04	<0.001
Breastfeeding (per 1-year increase)[f]	0.80	0.71, 0.89	0.85	0.73, 0.98	0.68	0.49, 0.94	0.45	0.27, 0.77	0.03
Tubal ligation	0.69	0.55, 0.85	0.86	0.65, 1.16	0.57	0.32, 1.00	0.51	0.25, 1.04	0.21
Hysterectomy	0.69	0.52, 0.92	0.77	0.53, 1.13	0.78	0.42, 1.44	0.57	0.23, 1.42	0.81
Estrogen use (per 5-year increase)[g]	1.36	1.13, 1.64	1.45	1.16, 1.81	2.33	1.53, 3.53	0.93	0.38, 2.26	0.08

Abbreviations: CI, confidence interval; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; RR, incidence rate ratio.
[a] Estimates were adjusted for all variables in the table, plus cohort (NHS or NHSII), parous (yes/no), menopausal status (postmenopause vs. premenopause/perimenopause), and missing data on breastfeeding duration (yes/no) because of noncompletion of questionnaire.
[b] Model excludes women with missing age at natural menopause because of hysterectomy prior to menopause.
[c] Includes borderline and invasive tumors.
[d] P value from likelihood ratio test comparing, for each covariate, the model with separate estimates for the serous invasive, endometrioid, and mucinous histologic subtypes with the model with a single estimate across the 3 subtypes.
[e] Current age (if premenopausal) or age at natural menopause minus (age at menarche + duration of oral contraceptive use in years + parity).
[f] Breastfeeding duration first collected in 1986 in the NHS and 1993 in the NHSII.
[g] Duration of postmenopausal use of unopposed estrogens.

body mass index, but these differences were not statistically significant.

Previous epidemiologic studies have reported differences in the risk factors for each histologic subtype of ovarian cancer, although most studies were retrospective and few reported a statistical test of differences in risk across subtypes. In a pooled analysis, parity and oral contraceptive use were inversely associated with all 4 major subtypes, although parity was most protective for endometrioid and clear-cell tumors, and breastfeeding was inversely

Table 4. Association Between Nonreproductive Exposures and Risk of Epithelial Ovarian Cancer, by Histologic Subtype, Among 108,446 Women in the NHS From 1976 to 2006 and 112,054 Women in the NHSII From 1989 to 2005[a]

	All Epithelial (n = 876)		Serous Invasive (n = 468)		Endometrioid (n = 134)		Mucinous[b] (n = 84)		P-Heterogeneity[c]
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	
Body mass index (per 5-kg/m^2 increase)	1.05	0.98, 1.12	0.97	0.88, 1.07	1.18	1.02, 1.38	0.90	0.72, 1.13	0.06
Activity (per 15-MET-hour/week increase)[d]	1.05	0.98, 1.13	1.08	0.98, 1.19	0.94	0.76, 1.16	0.82	0.61, 1.10	0.11
Talc use (≥once/week vs. <once/week)[e]	1.06	0.89, 1.28	1.06	0.84, 1.35	1.06	0.66, 1.69	1.50	0.84, 2.66	0.55
Past smoker	1.05	0.91, 1.22	1.09	0.89, 1.34	0.59	0.39, 0.90	1.54	0.94, 2.53	0.03
Current smoker	1.11	0.92, 1.35	1.14	0.88, 1.49	0.93	0.59, 1.47	1.52	0.85, 2.74	
Family history of breast cancer	1.29	1.07, 1.56	1.34	1.04, 1.73	1.94	1.24, 3.03	1.42	0.76, 2.63	0.38
Family history of ovarian cancer[f]	1.75	1.19, 2.57	1.85	1.13, 3.03	0.47	0.07, 3.39	4.50	1.76, 11.51	0.06

Abbreviations: CI, confidence interval; MET, metabolic equivalent task; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; RR, incidence rate ratio.
[a] Estimates were adjusted for all variables in the table, plus all covariates in the final reproductive model (Table 2) and variables for missing data on talc use or family history of ovarian cancer (yes/no).
[b] Includes borderline and invasive tumors.
[c] P value from likelihood ratio test comparing, for each covariate, the model with separate estimates for the serous invasive, endometrioid, and mucinous histologic subtypes with the model with a single estimate across the 3 subtypes.
[d] Cumulative average physical activity beginning in 1986 for the NHS and 1989 for the NHSII.
[e] Information on regular genital talc use available for NHS participants only; collected in 1982.
[f] Information on family history of ovarian cancer first collected in 1992 in the NHS and 1993 in the NHSII.

Table 5. AUC for Total Epithelial Ovarian Cancer and Each Histologic Subtype Among Women in the NHS From 1976 to 2006 and the NHSII From 1989 to 2005

Model	All Epithelial		Serous Invasive		Endometrioid		Mucinous[a]	
	No. of Cases	AUC	No. of Cases	AUC	No. of Cases	AUC	No. of Cases	AUC
Reproductive (Table 2)	924	0.624	496	0.614	139	0.714	86	0.678
Ovulatory years (Table 3)[b]	767	0.617	397	0.616	118	0.703	80	0.650
Reproductive + nonreproductive exposures (Table 4)	876	0.645	468	0.644	134	0.748	84	0.744
Ovulatory years + nonreproductive exposures[b,c]	731	0.643	378	0.652	114	0.746	78	0.719

Abbreviations: AUC, area under the receiver operating characteristic curve; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II.
[a] Includes borderline and invasive tumors.
[b] Excludes women with missing age at natural menopause because of hysterectomy prior to menopause.
[c] Results from this model are not shown.

associated with the serous, endometrioid, and mucinous subtypes but was most protective for mucinous cancers (6). These results, as well as the pooled associations for family history, body mass index, and smoking, were consistent with our study (6). Tubal ligation was inversely associated with serous and clear-cell cancers in the pooled analysis (6), but other studies have reported inverse associations for tubal ligation or hysterectomy and risk of endometrioid and/or mucinous tumors (8, 13, 14, 21). Age at menopause was associated with an increased risk of endometrioid tumors in a small study ($n = 41$ endometrioid cases) (22) but not in 2 other studies (7, 23), and estrogen use was more strongly positively associated with endometrioid cancers in some (24–26) but not all (13, 27) previous studies. Three studies of ovulatory years reported a positive association with nonmucinous cancers but no association with the mucinous subtype (9, 10, 14), similar to our study.

Among the nonreproductive exposures, recent physical activity was inversely associated with risk of all 4 histologic subtypes in one study, although the association was statistically significant for serous cancers only (28). Similarly, another study noted inverse associations with risk of serous, endometrioid, and mucinous tumors (29). However, prospective studies, including ours (30), generally have observed null or positive associations (31–33). Several previous studies of genital talc use, including an analysis in the NHS (34), observed a stronger positive association with serous or serous invasive cancers (35–38), although 2 studies reported no difference by subtype (39, 40) and 1 reported a positive association with mucinous tumors (38). Although our results generally are consistent with the existing literature, apparent differences, such as those for talc use, may be due to the limited number of cases of endometrioid or mucinous histology.

At one time, it was believed that the majority of epithelial ovarian cancers, regardless of histology, arose through transformation of the ovarian surface epithelium. However, growing evidence suggests a varied origin of these cancers; for example, high-grade serous carcinomas may arise in the distal fallopian tube (41–43). Morphologically, serous tumors resemble normal fallopian tube epithelium, endometrioid tumors resemble normal endometrium, and mucinous tumors resemble benign intestinal mucosa or cervical epithelium (4). In addition, there are similarities in gene expression between each subtype and its corresponding normal tissue (5).

The risk factor profiles we observed are consistent with evidence that each subtype resembles a different normal tissue. For example, parity, duration of breastfeeding, and smoking were inversely associated with risk of endometrioid tumors, whereas duration of estrogen use and body mass index were positively associated with risk. This pattern of risk factors is similar to that for endometrial cancer, which is influenced by estrogens and is positively associated with hormone-related exposures, most notably obesity and estrogen use (44). For the mucinous subtype, our results suggest that exposure to carcinogens and other chemicals (e.g., tobacco smoke or talc) may increase risk, whereas surgical procedures that decrease ovarian exposure to exogenous agents (e.g., tubal ligation or hysterectomy) may be protective. Although these results generally are not consistent with known risk factors for colon or cervical cancer (45, 46), evidence exists that smoking (47, 48) and exposure to certain chemicals (49–51) may increase risk of these cancers. The serous invasive subtype was associated with reproductive and hormonal exposures, including parity, duration of oral contraceptive use, and duration of estrogen use. Limited data are available on risk factors for fallopian tube carcinoma, although parity and tubal ligation appear to be protective (52). Information on the epidemiology of serous ovarian tumors may be informative for future research of fallopian tube primary carcinomas.

Strengths of our study include the prospective data with repeated measures for most exposures and the large combined study population. In addition, methods used in this analysis allowed for estimation of separate associations with each subtype simultaneously, as well as formal tests for differences across subtypes.

Although our analysis included a large number of epithelial cases, we had a limited number of cases with certain subtypes (e.g., clear-cell and noninvasive serous cancers). Furthermore, we classified histologic subtype based on a review of pathology reports rather than a central pathology review or immunostaining. Although this categorization likely resulted in some misclassification of histologic subtype, a validation study within the NHS found that histologic subtype based on central pathology review corresponded to

the pathology report for a high percentage of cases (17). The incomplete data for a few exposures, in particular talc use and family history of ovarian cancer, also are weaknesses because the limited data may have influenced the observed associations for these exposures. The association with talc use in our analysis differed from the association in a previous analysis of the NHS cohort (34), possibly because of a greater degree of exposure misclassification over 24 years of follow-up. However, the suggestive positive association with the mucinous subtype may reflect a longer latency period between talc exposure and development of mucinous tumors. Finally, the use of a single summary measure for certain exposures, such as physical activity, also may have limited our ability to detect an association. Additional analyses of different types/intensities of physical activity and risk of each subtype would help clarify this association.

In summary, our study provides additional evidence that associations with several ovarian cancer risk factors differ by histologic subtype and that these differences are consistent with known similarities between each subtype and a corresponding normal tissue. Differences in risk by subtype may help explain variability in the association with certain exposures across study populations, because the observed associations may differ depending on the distribution of the exposure and histologies. Future epidemiologic studies of ovarian cancer therefore should examine the histologic subtypes separately to determine whether heterogeneity in the association exists across subtypes. Analyses not taking into account differences in ovarian cancer risk by histologic subtype could be misleading.

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REPORTS

Prospective Study of Talc Use and Ovarian Cancer

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Background: **Perineal talc use has been associated with an increased risk of ovarian cancer in a number of case–control studies; however, this association remains controversial because of limited supporting biologic evidence and the potential for recall bias or selection bias in case–control studies. In this study, we conducted a prospective analysis of perineal talc use and the risk of ovarian cancer. *Methods:* The Nurses' Health Study is a prospective study of 121 700 female registered nurses in the United States who were aged 30–55 years at enrollment in 1976. Talc use was ascertained in 1982 by use of a self-administered questionnaire: after exclusions, 78 630 women formed the cohort for analysis. Three hundred seven epithelial ovarian cancers subsequently diagnosed in this cohort through June 1, 1996, were confirmed by medical record review and met inclusion criteria. Proportional hazards models by use of pooled logistic regression were used to derive relative risks (RRs) and 95% confidence intervals (CIs). *Results:* In 1982, 40.4% (n = 31 789) of the cohort reported ever using talc, and 14.5% (n = 11 411) reported ever using talc daily. We observed no overall association with ever talc use and epithelial ovarian cancer (multivariate RR = 1.09; 95% CI = 0.86–1.37) and no increase in risk of ovarian cancer with increasing frequency of use. There was a modest elevation in risk for ever talc use and invasive serous ovarian cancer (multivariate RR = 1.40; 95% CI = 1.02–1.91). The risk of epithelial ovarian cancer for talc users was not greater among women who had never had a tubal ligation (multivariate RR = 0.97; 95% CI = 0.71–1.32). *Conclusion:* Our results provide little support for any substantial association between perineal talc use and ovarian cancer risk overall; however, perineal talc use may modestly increase the risk of invasive serous ovarian cancer. [J Natl Cancer Inst 2000;92:249–52]**

Talc was originally implicated as a possible ovarian carcinogen because of its chemical similarity to asbestos, which has been linked to ovarian cancer in occupational settings and is associated with mesotheliomas histologically resembling epithelial ovarian cancers *(1–3)*. Perineal use of talcum powder has been positively associated with ovarian cancer risk in a number of case–control studies *(4–13)*, although the magnitude of the associations has been modest, with odds ratios ranging from 1.2 to 1.9, and not all results reached statistical significance *(5,6,8)*. Despite this relative consistency among studies, the limited supporting biologic evidence, together with the possibility of recall and selection bias in case–control studies *(1)*, has raised questions about the plausibility of the association. We, therefore, prospectively examined the relationship between perineal talc use and ovarian cancer risk in a large cohort of U.S. women.

Methods

The Nurses' Health Study, established in 1976, is a prospective cohort of 121 700 registered nurses living in 11 of the larger states in the United States. Questionnaires were mailed to married, female nurses aged 30–55 years, requesting information on health-related issues, including medical history and potential risk factors for cancer. Follow-up questionnaires have been mailed every 2 years to update information on exposures and to ascertain newly diagnosed diseases. The study was approved by the Human Research Committee at the Brigham and Women's Hospital, Boston, MA.

Ascertainment of cases. We sought medical records from all women who reported a diagnosis of ovarian cancer or who were deceased in each follow-up cycle. Records were reviewed by physicians unaware of exposure status. Histologic subtypes were determined from pathology reports, and epithelial ovarian cancers were classified as serous cancers (including cystadenocarcinoma and papillary adenocarcinoma), mucinous cancers (including adenocarcinoma and mucinous papillary adenocarcinoma), and endometrioid cancers (clear cell and other types, including mixed epithelial tumors). Borderline histologic tumors are included in the analysis. Deaths are reported by relatives and postal authorities, as well as a search of the National Death Index. Mortality follow-up is estimated to be 98% complete in this cohort *(14)*. Cases of epithelial ovarian cancer (International Classification of Diseases Code, ICD183.0), confirmed by medical record review or death certificate, occurring between the return of the 1982 questionnaire and June 1, 1996, were included in the analysis.

Exclusions. Women who did not respond to the question on talc use in 1982 were excluded from this analysis. We also excluded women who had reported a diagnosis of cancer (other than nonmelanoma skin cancer) before 1982, as well as women who reported bilateral oophorectomy, surgery with an unknown number of ovaries removed, and a history of radiation therapy. Validity of self-reported surgical menopause has been assessed previously, and agreement with medical records was more than 97% *(15)*. These exclusions were updated every 2 years. At baseline, 78 630 women were eligible for the analysis. The resulting population after exclusions contributed 984 212 person-years of follow-up and 307 cases of epithelial ovarian cancer.

Ascertainment of talc exposure. Use of talcum powder was ascertained on the 1982 questionnaire in the following ways: "Have you ever commonly used talcum, baby powder, or deodorizing powder *a)* to apply to perineal (private) area? No, daily, one to six times per week, or less than once per week or *b)* to apply on sanitary napkins? No, Yes." We classified "ever talc use" as ever talc use on either the perineal area or sanitary napkins.

Other covariates. Potential risk factors and confounders of the association between ovarian cancer and exposures of interest in this analysis also were obtained from the biennial questionnaires and were updated every 2 years where relevant. Oral contraceptive use was asked every 2 years from 1976 through 1982, by which time use was rare. Tubal ligation history was asked as part of a question on methods of contraception from 1976 through 1984, and, in 1994, women were asked if they had ever

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See "Notes" following "References."

had a tubal ligation and, if so, at what age. Family history of ovarian cancer was not asked until 1992. Parity was defined as the number of pregnancies lasting 6 months or more and was asked through 1984.

Statistical analysis. Incidence rates (number of cases for each category of exposure divided by person months of follow-up in that cycle) were calculated for each category, adjusting for age in 5-year intervals. Proportional hazards models by use of pooled logistic regression were used to derive relative risks (RRs) and 95% confidence intervals (CIs) of disease for each exposure category *(16)*. For age-adjusted analyses, we categorized variables as follows: parity (0, 1–2, or ≥3), oral contraceptive use (never, past, or current), tubal ligation (yes or no), postmenopausal hormone use (never, past, or current), cigarette smoking (never, past, or current), and body mass index, i.e., weight in kilograms/height in meters squared (<21, 21.0–22.9, 23.0–24.9, 25.0–28.9, or ≥29 kg/m^2). In multivariate analyses, we adjusted for age (years) and for potential risk factors by use of indicator variables for each category as described above, except for parity (0, 1–2, 3–4, or ≥5) and duration of oral contraceptive use (never or <3, 3–5, or >5 years), for which we used a larger number of categories to more appropriately control for confounding. In addition we controlled for age at menarche, duration of breast-feeding, and age at menopause. However, since this did not alter the estimates for talc use, further models did not control for these variables. Body mass index and duration of oral contraceptive use were also entered as continuous variables, and similar estimates were obtained. All RRs reported are multivariate unless otherwise stated. *P* values reported are two-sided.

Results

Three hundred seven women developed ovarian cancer in the cohort from 1982 through 1996 who responded to the 1982 questionnaire on talc use. In 1982, 40.4% (n = 31 789) of the baseline cohort reported ever using talc, of which 14.5% (n = 11 411) were ever daily talc users. Talc use was associated with higher body mass index and inversely associated with current cigarette smoking (Table 1).

We did not observe an overall association with ever use of talc and epithelial ovarian cancer (RR = 1.09; 95% CI = 0.86 1.37). There was also no elevation in risk among daily users of perineal talc, and no trend was seen with increasing frequency of use (Table 2). Talc use on sanitary napkins was inversely related to ovarian cancer, but the association was statistically nonsignificant. Exclusion of use of talc on sanitary napkins from the ever use of talc variable did not substantially alter the results. We also evaluated the risk for women who used both perineal talc and talc on sanitary napkins but did not see an effect compared with never users of talc (RR = 0.90; 95% CI = 0.59–1.37).

When we stratified by histologic subtype, we observed a modest increase in risk for ever talc use for serous invasive cancers (RR = 1.40; 95% CI = 1.02–1.91) but not for all serous cancers (including borderline cancers), endometrioid cancers, or mucinous cancers (Table 3). For women who reported ever daily use of talc, the RR of invasive serous cancer was 1.49 (95% CI = 0.98–2.26). The RRs for ever talc users of less than once per week and one to six times per week were 1.29 (95% CI = 0.81–2.04) and 1.49 (95% CI = 0.77–2.11), respectively (*P* for trend = .05).

Table 1. Age-standardized prevalence of ovarian cancer risk factors according to perineal talc use in 1982*

	Ever perineal talc use, %† (n = 31 789)	No perineal talc use, % (n = 46 841)
Parity		
0	6.3	6.4
1–2	35.0	35.2
≥3	58.7	58.4
Oral contraceptive use		
Current	0.5	0.6
Past	49.2	49.8
Never	50.4	49.6
Hormone use, postmenopausal women only		
Current	12.1	12.9
Past	20.5	20.4
Never	67.4	66.7
Tubal ligation, yes	17.6	17.6
Cigarette smoking		
Never	44.9	43.2
Past	30.3	28.3
Current	24.9	28.5
Body mass index quintiles, kg/m^2		
<21.0	16.0	22.1
21.0–22.9	20.9	25.4
23.0–24.9	20.1	20.6
25.0–28.9	22.8	19.6
≥29	19.8	12.0

*Numbers do not always add up to 100% because of missing data or rounding.
†Ever talc use coded as either talc use on perineal area or talc use on sanitary napkins.

Table 2. Talc use and ovarian cancer: 1982 through 1996 (all subtypes included)*

	No. of cases	Person-years	Age-adjusted RR (95% CI)	Multivariate RR† (95% CI)
Talc use on perineum				
Never	186	608 020	1.0 (referent)	1.0 (referent)
<1/wk	43	128 923	1.10 (0.79–1.53)	1.14 (0.81–1.59)
1–6/wk	30	105 186	0.95 (0.65–1.40)	0.99 (0.67–1.46)
Daily	48	142 083	1.09 (0.79–1.49)	1.12 (0.82–1.55)
Talc use on sanitary napkins				
No	242	781 421	1.0 (referent)	1.0 (referent)
Yes	32	111 399	0.89 (0.62–1.29)	0.89 (0.61–1.28)
Ever perineal talc use				
No	179	586 758	1.0 (referent)	1.0 (referent)
Yes	128	397 454	1.05 (0.84–1.32)	1.09 (0.86–1.37)
Talc use, perineal and sanitary napkins				
None	179	586 758	1.0 (referent)	1.0 (referent)
Either talc use on perineum or use on sanitary napkins	103	307 317	1.11 (0.87–1.41)	1.15 (0.90–1.46)
Use on both sanitary napkins and perineum	25	90 137	0.89 (0.58–1.35)	0.90 (0.59–1.37)

*RR = relative risk; CI = confidence interval.
†Multivariate analyses control for age (years), parity (0, 1–2, 3–4, or ≥5), duration of oral contraceptive use (never or <3 y, 3–5 y, or >5 y), body mass index (body weight in kilograms/height in meters squared: <21, 21.0–22.9, 23.0–24.9, 25.0–28.9, or ≥29 kg/m^2), tubal ligation history (yes or no), smoking status (never, past, or current), and postmenopausal hormone use (never, past, or current).

Table 3. Talc use and ovarian cancer: 1982–1996 (by histologic subtype)*

Histologic subtype	No. of cases	Person-years	Age-adjusted RR (95% CI)	Multivariate RR† (95% CI)
All serous cancers, ever perineal talc use				
No	101	586 771	1.0 (referent)	1.0 (referent)
Yes	84	397 459	1.23 (0.92–1.64)	1.26 (0.94–1.69)‡
Serous invasive cancers, ever perineal talc use				
No	84	586 771	1.0 (referent)	1.0 (referent)
Yes	76	397 459	1.33 (0.98–1.82)	1.40 (1.02–1.91)‡
Endometrioid cancers, ever perineal talc use				
No	26	586 771	1.0 (referent)	1.0 (referent)
Yes	16	397 459	0.91 (0.49–1.69)	0.91 (0.49–1.87)
Mucinous cancers, ever perineal talc use				
No	30	586 771	1.0 (referent)	1.0 (referent)
Yes	20	397 459	0.98 (0.56–1.73)	0.93 (0.53–1.66)

*RR = relative risk; CI = confidence interval.

†Multivariate analyses controlling for age (years), parity (0, 1–2, or ⩾3), oral contraceptive use (never or ever), and tubal ligation history (yes or no).

‡Multivariate analyses control for age (years), parity (0, 1–2, 3–4, or ⩾5), duration of oral contraceptive use (never or <3 y, 3–5 y, or >5 y), body mass index (body weight in kilograms/height in meters squared: <21, 21.0–22.9, 23.0–24.9, 25.0–28.9, or ⩾29 kg/m^2), tubal ligation history (yes or no), smoking status (never, past, or current), and postmenopausal hormone use (never, past, or current).

Because the talc hypothesis depends on the ability of fibers to migrate up a patent genital tract to the ovaries, we evaluated the risk among women who had reported a tubal ligation and those who had not. Women who were ever talc users and had never had a tubal ligation were not at increased risk of epithelial ovarian cancer compared with women who had not used talc (RR = 0.97; 95% CI = 0.71–1.32). There was no evidence of heterogeneity of RRs between women who had a tubal ligation and women who did not. In addition, when women who had had a tubal ligation or simple hysterectomy were excluded from the analysis, the RR for ever talc use was 1.15 (95% CI = 0.89–1.49). For serous invasive cancers, the RR for women who had never had a tubal ligation was similar to that for women without a tubal ligation; however, the number of case patients who had had a tubal ligation was small (data not shown).

Cosmetic talc may have been more likely to contain asbestos fibers prior to 1976, before voluntary guidelines were proposed *(9)*. As a proxy for early talc use, we assessed risk among women 45 years old or older in 1982. There was no evidence that older women in 1982 were at greater risk of ovarian cancer overall; the RR for ever talc use compared with never talc use for women under 45 years was 0.95 (95% CI = 0.59–1.53) and among women 45 years old or older was 1.13 (95% CI = 0.86–1.47). However, women 45 years old or older in 1982 who ever used talc had a higher risk of serous invasive cancer (RR = 1.51; 95% CI = 1.07–2.15). There was no evidence of effect modification by oral contraceptive use, body mass index, or cigarette smoking for epithelial cancers overall.

Discussion

To our knowledge, this is the first prospective analysis of talc use and ovarian cancer, and it addresses some of the potential limitations of previous case–control studies. Because we ascertained talc exposure prior to case diagnosis, the possibility for recall bias, which has been raised as a potential explanation for previous positive findings in case–control studies *(1)*, is eliminated, and selection bias is reduced. We controlled for known or suspected ovarian cancer risk factors in the analysis, such as parity, oral contraceptive use, tubal ligation history, and body mass index, reducing the potential for uncontrolled confounding.

However, there are several important limitations to our study. The questions on talcum powder use referred to ever use, and we cannot determine the age at which women began using talc or the duration of use. Thus, we were unable to assess the potential effect of talc use before first pregnancy, which has been shown to be a stronger risk factor for ovarian cancer than use after pregnancy in one study *(13)*. The number of lifetime applications of talc has also been associated with increased risk of ovarian cancer in some previous studies *(9,13)*. Our relatively short follow-up period may be inadequate to detect an association if the latency for development of ovarian cancer is more than 15 years. Although we controlled for tubal ligation history, the tubal ligation question was asked as part of a question on contraceptive use; therefore, postmenopausal women and some premenopausal women who were not sexually active may not have responded to the question. Substantial residual confounding is unlikely, since there was no overall association between talc use and tubal ligation in this study. In addition, we excluded women who were postmenopausal in 1976 from analyses stratified by tubal ligation history. Finally, the prevalence of talc use in our study is somewhat higher than that in other studies and may reflect the fact that we asked about frequency of ever use rather than current regular use; this may have contributed to an attenuation of risk due to misclassification of exposure.

The potential effect of talc on the ovaries depends on migration of talc fibers through a patent genital tract, and we would, therefore, expect a stronger association among women without a tubal ligation who had used talc. However, no effect modification was seen by history of tubal ligation. Because we did not have the date of tubal ligation, some women may have begun talc use only after tubal ligation, potentially resulting in misclassification of talc use and attenuation of the RRs.

Since the first study showing an almost twofold increase in risk of ovarian cancer with any perineal talc use *(4)*, most case–control studies have demonstrated positive associations with talc use *(4–13)*, although not all have been statistically significant *(5,6,8)*. Several studies *(9,17–20)* found no overall association between any genital talc use and ovarian cancer. We did not observe a dose–response relationship with talc use, and previous studies also have been inconsistent in this regard. Some studies *(9,13,17)* have demonstrated statistically insignificant trends in risk with increased frequency of talc use, duration of use, and measures of "total lifetime applications," while other studies *(6,8)* have not observed a statistically significant dose response.

With regard to histologic subtypes, a recent study by Cramer et al. *(13)* observed the greatest risk for talc use and invasive serous cancer; however, other

studies found increased risks for endometrioid cancers *(9,12)*, serous cancers *(7)*, and invasive cancers of all subtypes *(12)*. Since serous cancers, which account for more than half of all invasive ovarian cancers, most resemble mesotheliomas, it could be hypothesized that this subtype may be most likely associated with talc use. In our stratification by subtype, we did observe a modest positive association with serous invasive cancers and ever talc use as well as a borderline significant trend for increasing frequency of ever use.

The biologic evidence for the association of talc and ovarian cancer is incomplete. Asbestos has been linked to ovarian cancer in occupational settings and is associated with peritoneal tumors similar to ovarian cancer *(2,3,21)*. Because of the chemical similarity of talc and asbestos, talc also has been implicated as a possible ovarian carcinogen. Talc is able to migrate through the genital tract and gain access to the ovaries because talc fibers have been detected in benign and malignant ovarian tissue *(22)*, although no relation between reported levels of talc exposure and ovarian talc counts has been observed *(23)*. There have been few studies *(24,25)* of talc exposure in animals, and these studies have not demonstrated an increase in ovarian cancer among animals subjected to chronic talc exposure. These data should be interpreted cautiously because there are important anatomic and physiologic differences between rodents and humans, and talc in animals is often administered at high dose via aerosol exposure *(24)*.

In summary, we did not observe an overall association between epithelial ovarian cancer and ever use of talc, and there was no apparent dose response, although we lacked information on duration of talc use. In analyses stratified by histologic subtype, we observed a modest positive association between invasive serous cancer and ever talc use. Our results provide little support for any substantial association between perineal talc use and ovarian cancer risk overall; however, perineal talc use may modestly increase the risk of invasive serous ovarian cancers.

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Notes

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Research Article

Cancer Epidemiology, Biomarkers & Prevention

African Americans and Hispanics Remain at Lower Risk of Ovarian Cancer Than Non-Hispanic Whites after Considering Nongenetic Risk Factors and Oophorectomy Rates

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Abstract

Background: Risk factors for invasive epithelial ovarian cancer (IEOC) among Hispanics and African Americans are understudied despite notable differences in incidence relative to non-Hispanic whites.

Methods: We used multivariate logistic regression to examine parity, oral contraceptive use, tubal ligation, endometriosis, family history of ovarian cancer, and talc use and risk of IEOC among Hispanics (308 cases and 380 controls), African Americans (128 cases and 143 controls), and non-Hispanic whites (1,265 cases and 1,868 controls) using four case–control studies we conducted in Los Angeles County. We expressed each of these factors in the form of increasing risk and calculated population attributable risk percentage (PAR%) estimates for the six risk factors separately and jointly in the three groups.

Results: The risk associations with these six well-accepted factors were comparable in the three groups. The significant racial/ethnic differences in the prevalence of these factors and differences in their oophorectomy rates explained 31% of the lower incidence in African Americans compared with non-Hispanic whites, but only 13% of the lower incidence in Hispanics. The PAR%s ranged from 27.5% to 31.0% for no tubal ligation, 15.9% to 22.2% for not using oral contraceptives, and 12.2% to 15.1% for using talc in the three groups.

Conclusions: All six risk factors are comparably important in the three groups. Differences in the prevalence of these factors and their oophorectomy rates explained approximately one third of the difference in incidence between African Americans and non-Hispanic whites.

Impact: Devising strategies to lessen the burden of IEOC will be applicable to all three racial/ethnic groups. *Cancer Epidemiol Biomarkers Prev; 24(7); 1094–100. ©2015 AACR.*

Introduction

In the United States in the period 2000 to 2009, the annual age-adjusted incidence rate of invasive epithelial ovarian cancer (IEOC) was highest in non-Hispanic whites (14.3/100,000), intermediate in Hispanics (12.1/100,000; 15% lower than the rate in non-Hispanic whites) and lowest in African Americans (10.2/100,000; 29% lower than the rate in non-Hispanic whites; ref. 1). Epidemiologic studies of ovarian cancer risk have focused primarily on non-Hispanic white women; reasons for the racial/ethnic differences in incidence are not well understood.

A number of risk factors—first-degree family history of ovarian cancer, endometriosis, and use of talc—and protective factors—parity, use of oral contraceptives, and tubal ligation—have been unequivocally associated with ovarian cancer in non-Hispanic whites. There is virtually no information on ovarian cancer risk factors in Hispanics. A small number of Hispanic cases ($n = 42$) were included in an ovarian cancer case–control study conducted in the Central Valley of California, but only results on talc use were reported separately in Hispanics (35.7% in cases vs. 26.9% in controls; ref. 2). A hospital-based case–control study in Mexico compared risk factors between 84 ovarian cancer cases and control women selected from an outpatient clinic (3): Parity and use of oral contraceptives were significantly inversely associated with risk but information on other factors has not been presented.

Risk factors for ovarian cancer among African Americans have been examined in three reports (4–6). The Collaborative Analysis of U.S. Case–Control Studies of Ovarian Cancer included seven studies with a total of 110 ovarian cancers (72 invasive, 35 borderline, and 3 unknown) in African-American women (4). Ness and colleagues (5) reported on risk of ovarian cancer among 84 African-American women with invasive or borderline cancers (numbers of each not specified) from their Delaware Valley case–control study. More recently, Moorman and colleagues (6) reported results from 111 African Americans with invasive ovarian cancer from their North Carolina ovarian cancer case–control study. Reduced risk from increased parity and oral contraceptive use were found in all three studies. Tubal ligation was found to be significantly inversely associated with risk in both of the studies that reported on this factor (5, 6). The results regarding family history are unclear. John and colleagues (4) did not report on family history. Ness and colleagues found that a family history of ovarian cancer was inversely associated with risk in African

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Americans, but this was based on sparse numbers (1.2% of cases vs. 2.0% of controls), a finding contrary to the strong increased risk found in non-Hispanic whites (4.6% of cases vs. 1.9% of controls; ref. 5). Family history of ovarian cancer was not reported in the North Carolina study, but family history of breast or ovarian cancer was a significant risk factor for African Americans (6).

The literature on causes of IEOC in Hispanics and African Americans is, therefore, very limited and it remains unclear to what extent the differences in the prevalence of ovarian cancer risk factors explain the differences in incidence between these three racial/ethnic groups. During the period 1992 to 2008, we conducted four IEOC case–control studies in Los Angeles County designed to elucidate risk factors for the disease and to evaluate differences in risk across non-Hispanic whites, Hispanics, and African Americans.

Materials and Methods

The results presented here are based on pooling the questionnaire data from these four studies, which used identical data collection methods as regards the factors discussed here; comprehensive details of these methods have been published (7–9). These studies were approved by the University of Southern California Institutional Review Board, and written informed consent was obtained from each patient and control before her interview.

Case ascertainment

For all studies, newly diagnosed histologically confirmed IEOC cases were identified from the USC Cancer Surveillance Program, which is the Los Angeles County SEER Program. Eligible patients were female residents of Los Angeles County of self-reported non-Hispanic white, Hispanic, or African-American race/ethnicity. Cases were eligible for inclusion in the study if they were between 18 and 74 years of age at diagnosis (up to age 79 for cases diagnosed between 2003 and 2008). A total of 3,370 patients met the study criteria (2,580 non-Hispanic whites, 506 Hispanics, 284 African Americans). Overall, 15.7% of patients (17.2% non-Hispanic whites, 8.5% Hispanics, and 15.5% African Americans) declined to be interviewed, 16.9% had died or were too ill to be interviewed (17.8% non-Hispanic whites, 12.1% Hispanics, and 17.6% African Americans), and 11.4% could not be located or had moved out of Los Angeles County (10.2% non-Hispanic whites, 14.0% Hispanics, and 17.6% African Americans). We were thus able to carry out in-person interviews with 1,886 patients (1,415 non-Hispanic whites, 331 Hispanics, and 140 African Americans), representing 63.2% participation rate of the patients approached (61.1% non-Hispanic whites, 76.1% Hispanics, and 59.8% African Americans). The response rate was higher for patients diagnosed with localized cancer (69%) compared with those with more advanced stage at diagnosis (61%). Response rates were highest for those diagnosed under age 60 (70%), intermediate for those ages 60 to 69 (59%), and lowest for those ages 70+ (47%) at diagnosis. In this analysis, we excluded 185 patients who had a previous cancer (excluding nonmelanoma skin cancer) or had prior bilateral oophorectomy and the final analysis was based on 1,701 patients (1,265 non-Hispanic whites, 308 Hispanics, and 128 African Americans).

Control ascertainment

Controls were residents of Los Angeles County with at least one intact ovary identified using a well-tested neighborhood control selection algorithm (8–10). Neighborhood controls were individually matched to cases on race/ethnicity and year of birth (±5 years); they represented essentially all the controls interviewed. In one study, selection of controls for cases >65 years of age was augmented, if necessary, by using lists of female residents of Los Angeles County provided by the Health Care Financing Administration, matched to the case on zip code, race/ethnicity, and year of birth closest to the case's year of birth (8). Overall, 70% of the non-Hispanic white, Hispanic, and African-American controls interviewed were the first identified control.

Data collection

In-person interviews were conducted using standardized questionnaires that included the use of a life calendar. The core questions on the risk factors presented here were identical in the four studies. The questionnaire covered events up to 12 months before a case's diagnosis date and a similar reference date for the controls.

The demographic, lifestyle, and medical history variables considered in this analysis include race/ethnicity (African American, Hispanic, and non-Hispanic white), age at diagnosis, parity, oral contraceptive use, tubal ligation, self-reported physician-diagnosed endometriosis, first-degree family history of ovarian cancer, and genital talc use.

Statistical analysis

We used standard statistical methods, including multivariate logistic regression, using the statistical package programs STATA 12 (StataCorp) and SAS 9.2 (SAS Institute Inc.). Although the studies were designed as matched case–control studies, at the termination of the particular studies, some cases had not been matched to a control and there were some controls whose cases had to be excluded after they completed the interview, because they were ineligible for the current analysis (e.g., not IEOC or did not live in Los Angeles County at the time of diagnosis). In this report, we have used all interviewed cases and controls by adopting a stratified multivariate logistic regression analysis approach with joint stratification for the three race/ethnicity groups, age group (<30, 5-year age groups to age 79), interviewer, and study. Analysis focused on the following factors: nulliparity (yes/no), oral contraceptive use (yes/no; no included never and <1 year of use), tubal ligation (yes/no), history of endometriosis (yes/no), family history of ovarian cancer (mother or sister; yes/no), and history of genital talc use (yes/no; no included never and <1 year of use). The logistic regression analysis also adjusted for menopausal status [premenopausal, natural menopause age ≤49, natural menopause age 50–54, natural menopause ≥55, surgical menopause (simple hysterectomy only) age ≤49, surgical menopause ≥50, other], age at menarche (≤11, 12, 13, ≥14), hormone therapy use (none, former or current estrogen + progestin, former or current estrogen alone), body mass index (BMI; kg/m^2; ≤22, >22–24, >24–28, >28), family income (≤40,000, >40,000 to ≤64,000, >64,000 to ≤100,000, >100,000, do not know) and education (high school or less, some college, college or higher). ORs—and corresponding 95% confidence intervals (CI)—were calculated as estimates of the relative risks (RR). All statistical significance values (*P* values) quoted are two-sided.

Population attributable risk percentages (PAR%s), defined as the percentages of disease in the population that are attributable to a given risk factor (or set of risk factors), were calculated using the method of Bruzzi and colleagues (11). These authors showed that PAR%s could be calculated from a case–control study using

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the estimated RRs applied to the cases only. This approach is of particular value to our analysis as it only requires the cases to be a representative sample from the population at risk. This method uses the individual data on each case to calculate the expected fraction of the cases that would not have occurred if the risk factors being considered were at their baseline values, and this fraction was then used to calculate the PAR%. For a single risk factor, the confidence limit for the PAR% was obtained by repeating the calculation using the lower (and upper) confidence bound of the OR for the particular factor in this calculation. For multiple risk factors, the confidence bounds for the PAR% were obtained by simulation: drawing repeated random samples from the mean and covariance matrix of the log ORs from the logistic regression fit and calculating a PAR% from that sample—the 95% CI bounds were taken as the 2.5% and 97.5% values from the repeated samples. In our simulation analyses, we used 5,000 repeats.

Published incidence rates for IEOC make no adjustment for the number of women who have had their ovaries (and fallopian tubes) removed. Writing h for the proportion of women who have had a hysterectomy and t for the proportion of hysterectomies that include removal of the ovaries (oophorectomy), an incidence rate r is approximately adjusted (not accounting for age at oophorectomy) for the oophorectomy rate as follows:

$$r_{\text{adj-ooph}} = r/(1 - h \times t) \quad \text{(A)}$$

If a population incidence rate (or an oophorectomy adjusted incidence rate) r is associated with a PAR% p for a single risk factor (or a group of risk factors) then the expected incidence rate if the population was at the baseline risk of the risk factor is:

$$r_{\text{adj-PAR\%}} = r \times (1 - p/100) \quad \text{(B)}$$

Results

This analysis was based on 1,701 women diagnosed with IEOC (1,265 non-Hispanic whites, 308 Hispanics, and 128 African Americans) and 2,391 control women (1,868 non-Hispanic whites, 380 Hispanics, and 143 African Americans). The distribution of IEOC by histology, stage at diagnosis and differentiation did not differ significantly between the three groups (Table 1). The majority of IEOC in the three racial/ethnic groups was of serous cell type, distant stage at diagnosis, and poorly differentiated.

The prevalence of the risk factors, including the average number of births, duration of oral contraceptive use, and duration of talc use in the three groups of controls and cases, are shown in Table 2. All six factors are presented in the manner of being associated with increasing risk; that is, the factors that are inversely associated with risk are presented in the form of their absence being a risk factor, for example, the decreased risk in parous women is presented as a risk in nulliparous women. This was done to allow the presentation of PAR%s in a standard fashion.

With the exception of family history of ovarian cancer, the prevalence of the other risk factors differed significantly between the three racial/ethnic groups of control women (Table 2, top). The prevalence of no tubal ligation was 69.2% in African-American, 73.7% in Hispanic, and 85.9% in non-Hispanic white control women ($P_{2df} < 0.0001$). Nulliparity and history of endometriosis was highest in non-Hispanic whites, intermediate in African Americans, and lowest in Hispanics (23.7%, 16.8%, and 13.7% for nulliparity, $P_{2df} < 0.001$; 7.5%, 5.6%, and 3.4% for endometriosis, $P_{2df} = 0.008$). No oral contraceptive use (no/<1 year) was highest in Hispanics (54.7%), followed by African Americans (47.6%), and lowest in non-Hispanic whites (41.5%; $P_{2df} < 0.001$). Talc use was more common in African-American women (44.1%) than in non-Hispanic whites (30.4%) or Hispanics (28.9%; $P_{2df} = 0.001$). Similar patterns of differences in these risk factors between the three racial/ethnic groups of IEOC patients were found (Table 2, bottom).

As expected, each of the six risk factors had statistically significant independent effects on risk in non-Hispanic whites. Risk patterns in Hispanics paralleled those in non-Hispanic whites (Table 3), although the elevated risks with endometriosis and family history of ovarian cancer did not achieve statistical significance. In African Americans, family history of ovarian cancer was associated with a more than 7-fold increased risk, but the CI was wide (OR, 7.84; 95% CI, 1.66–37.0). The associations with parity, oral contraceptive use, tubal ligation, endometriosis, and talc use in African Americans are all in agreement with the risks found in non-Hispanic whites, although none were statistically significant.

Table 1. Tumor characteristics of invasive ovarian cancer in non-Hispanic whites, Hispanics, and African Americans: Los Angeles County Ovarian Cancer Study

	Non-Hispanic whites $N = 1{,}265$	Hispanics $N = 308$	African Americans $N = 128$
Age, y			
<30	12 (0.9%)	5 (1.6%)	1 (0.8%)
30–34	14 (1.1%)	11 (3.6%)	2 (1.6%)
35–39	33 (2.6%)	10 (3.2%)	3 (2.3%)
40–44	58 (4.6%)	31 (10.1%)	13 (10.2%)
45–49	144 (11.4%)	36 (11.7%)	17 (13.3%)
50–54	194 (15.3%)	60 (19.5%)	25 (19.5%)
55–59	186 (14.7%)	46 (14.9%)	18 (14.1%)
60–64	193 (15.3%)	43 (14.0%)	24 (18.8%)
65–69	179 (14.2%)	29 (9.4%)	15 (11.7%)
70–74	160 (12.6%)	23 (7.5%)	8 (6.3%)
75–79	92 (7.3%)	14 (4.5%)	2 (1.6%)
Histology			
Serous	721 (57.0%)	179 (58.1%)	71 (55.5%)
Mucinous	85 (6.7%)	26 (8.4%)	12 (9.4%)
Endometrioid	153 (12.1%)	34 (11.0%)	14 (10.9%)
Clear cel	75 (5.9%)	14 (4.5%)	4 (3.1%)
Epithelia	40 (3.2%)	13 (4.2%)	2 (1.6%)
Undifferentiated/poorly	53 (4.2%)	12 (3.9%)	10 (7.8%)
Other	131 (10.4%)	28 (9.1%)	14 (10.9%)
Not known	7 (0.6%)	2 (0.6%)	1 (0.8%)
P_{3df}[a,b]		0.54	0.40
Stage			
Localized	216 (17.1%)	58 (18.8%)	30 (23.4%)
Regional	170 (13.4%)	49 (15.9%)	12 (9.4%)
Distant	853 (67.4%)	197 (64.0%)	83 (64.8%)
Not known	26 (2.1%)	4 (1.3%)	3 (2.3%)
P_{2df}[a,c]		0.38	0.12
Differentiation			
Well	119 (9.4%)	29 (9.4%)	9 (7.0%)
Moderately well	235 (18.6%)	53 (17.2%)	28 (21.9%)
Poorly	502 (39.7%)	119 (38.6%)	46 (35.9%)
Undifferentiated	170 (13.4%)	33 (10.7%)	16 (12.5%)
Not known	239 (18.9%)	74 (24.0%)	29 (22.7%)
P_{3df}[a,b]		0.81	0.63

[a]P value comparing non-Hispanic whites with each of the other two groups separately.
[b]P value based on cases of serous, mucinous, endometrioid, and clear-cell histology only.
[c]P value excluding cases with no known histology or stage of cancer at diagnosis.

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Table 2. Prevalence of risk factors in non-Hispanic white, Hispanic, and African-American control women (top) and ovarian cancer cases (bottom)

Factors	Non-Hispanic whites	Hispanics	African Americans	P1[b]	P2[c]	P3[d]
Controls[a]						
Nulliparous (%)	23.7%	13.7%	16.8%	<0.001	0.076	0.45
Mean # births among parous (SD)	2.5 (1.3)	3.0 (1.7)	2.7 (1.5)	<0.001	0.03	0.15
Oral contraceptive use (no/<1 year; %)	41.5%	54.7%	47.6%	<0.001	0.19	0.17
Mean # months of OC use among users (SD)	95.9 (74.9)	81.0 (67.0)	93.1 (74.2)	0.014	0.75	0.21
No tubal ligation (%)	85.9%	73.7%	69.2%	<0.001	<0.001	0.36
Endometriosis (%)	7.5%	3.4%	5.6%	0.006	0.50	0.38
Family history of ovarian cancer (%)	2.5%	3.4%	2.8%	0.37	0.98	0.93
Talc use ≥1 year (%)	30.4%	28.9%	44.1%	0.61	0.0001	0.002
Mean # years of talc use among users (SD)	23.9 (17.4)	21.3 (16.7)	22.9 (17.0)	0.15	0.67	0.55
Cases[e]						
Nulliparous (%)	27.8%	17.9%	16.4%	<0.001	0.007	0.82
Mean # births among parous (SD)	2.5 (1.2)	3.1 (1.7)	2.8 (1.6)	<0.001	0.003	0.24
Oral contraceptive use (no/< 1 year; %)	57.4%	69.8%	50.0%	<0.001	0.13	<0.001
Mean # months of OC use among users (SD)	73.4 (61.1)	59.8 (53.1)	75.7 (66.7)	0.044	0.75	0.10
No tubal ligation (%)	90.6%	83.8%	80.5%	<0.001	<0.001	0.49
Endometriosis (%)	11.1%	5.5%	9.4%	0.005	0.66	0.21
Family history of ovarian cancer (%)	5.1%	4.9%	7.0%	0.96	0.48	0.50
Talc use ≥1 year (%)	41.2%	38.6%	47.7%	0.45	0.19	0.10
Mean # years of talc use among users (SD)	27.5 (18.4)	21.6 (16.9)	26.6 (18.2)	0.001	0.71	0.069

[a]Controls included: 1,868 non-Hispanic whites, 380 Hispanics, and 143 African Americans.
[b]P_{1df} for differences between non-Hispanic whites and Hispanic controls (top)/P_{1df} for differences between non-Hispanic whites and Hispanic cases (bottom).
[c]P_{1df} for differences between non-Hispanic whites and African American controls (top)/P_{1df} for differences between non-Hispanic whites and African American cases (bottom).
[d]P_{1df} for differences between Hispanic and African American controls (top)/P_{df} for differences between Hispanic and African American cases (bottom).
[e]Cases included: 1,265 non-Hispanic whites, 308 Hispanics, and 128 African Americans.

The adjusted ORs for the three racial/ethnic groups combined are also shown in Table 3.

The first three columns of Table 4 show that these six factors together accounted for 57.9% of IEOCs in non-Hispanic whites compared with 56.1% in Hispanics and 53.8% in African Americans based on the race/ethnicity-adjusted OR estimates shown in Table 3 (last column). The PAR% due to "no tubal ligation" was large in all three racial/ethnic groups, ranging from 27.5% to 31.0%, followed by "no oral contraceptive use" (ranging from 15.9% to 22.2%), and talc use (ranging from 12.2% to 15.1%). The PAR% for nulliparity was 8.9% in non-Hispanic whites, but lower in Hispanics (5.7%) and African Americans (5.5%). The PAR%s for endometriosis (ranging from 2.0% to 4.0%) and family history of ovarian cancer (ranging from 2.7% to 3.9%) were more modest. The large "no tubal ligation" PAR% is due to relatively high prevalence in the IEOC patients (Table 2, bottom);

Table 3. Mutually adjusted ORs[a] for invasive ovarian cancer in Los Angeles County non-Hispanic whites, Hispanics, and African Americans

	Non-Hispanic whites (1,265/1,868)		Hispanics (308/380)		African Americans (128/143)		All (1701/2391)	
	ca/co	OR (95% CI)	ca/co	OR (95% CI)	ca/co	OR (95% CI)	ca/co	OR (95% CI)
Live-births								
Yes	913/1,426	1.00	253/328	1.00	107/119	1.00	1,273/1,873	1.00
No	352/442	1.43 (1.19–1.73)	55/52	2.22 (1.28–3.84)	21/24	1.42 (0.54–3.75)	428/518	1.47 (1.24–1.75)
Per birth		0.70 (0.58–0.84)		0.45 (0.26–0.78)		0.70 (0.27–1.86)		0.68 (0.57–0.81)
Oral contraceptive (OC)								
Yes	539/1,092	1.00	93/172	1.00	64/75	1.00	696/1,339	1.00
None/<1 year	726/776	1.55 (1.31–1.84)	215/208	1.29 (0.87–1.92)	64/68	1.30 (0.64–2.63)	1,005/1,052	1.47 (1.26–1.70)
Per 5 years OC		0.64 (0.54–0.76)		0.77 (0.52–1.15)		0.77 (0.38–1.55)		0.68 (0.59–0.79)
Tubal ligation								
Yes	119/263	1.00	50/100	1.00	25/44	1.00	194/407	1.00
No	1,146/1,605	1.41 (1.10–1.81)	258/280	1.71 (1.07–2.74)	103/99	1.65 (0.73–3.74)	1,507/1,984	1.52 (1.23–1.87)
Endometriosis								
No	1,125/1,728	1.00	291/367	1.00	116/135	1.00	1,532/2,230	1.00
Yes	140/140	1.51 (1.15–1.98)	17/13	2.21 (0.89–5.48)	12/8	1.74 (0.45–6.74)	169/161	1.56 (1.21–2.00)
First-degree family history of ovarian cancer								
No	1,200/1,822	1.00	293/367	1.00	119/139	1.00	1,612/2,328	1.00
Yes	65/46	2.12 (1.40–3.21)	15/13	2.38 (0.94–6.01)	9/4	7.84 (1.66–37.0)	89/63	2.26 (1.58–3.25)
Genital talc use								
None/<1 year	744/1,300	1.00	189/270	1.00	67/80	1.00	1,000/1,650	1.00
Yes	521/568	1.41 (1.21–1.67)	119/110	1.77 (1.20–2.62)	61/63	1.56 (0.80–3.04)	701/741	1.46 (1.27–1.69)
Per 5 years talc		1.14 (1.08–1.21)		1.18 (1.02–1.36)		1.15 (0.90–1.47)		1.14 (1.09–1.20)

[a]Race/ethnic specific multivariate logistic regression analyses were jointly stratified for age group (<30, 5-year age groups to age 79), interviewer and study, and adjusted for menopausal status, age at menarche, hormone therapy use, BMI, income, education, and each of the six factors shown. In analyses on "all subjects," we also jointly stratified by race/ethnicity.

Response to FDA Request for Information on Talc

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Table 4. Ovarian cancer PAR%s and 95% CI in Los Angeles County non-Hispanic whites, Hispanics, and African Americans[a]

	Using race-adjusted ORs[a]		
	Non-Hispanic whites PAR%[b]	Hispanics PAR%[b]	African Americans PAR%[b]
No live birth	8.9%	5.7%	5.3%
	5.3%–11.9%	3.4%–7.6%	3.1%–7.0%
No/<1 year oral contraceptives	18.3%	22.2%	15.9%
	12.0%–23.7%	14.5%–28.8%	10.4%–20.7%
No tubal ligation	31.0%	28.7%	27.5%
	17.2%–42.3%	15.9%–39.1%	15.2%–37.5%
Yes endometriosis	4.0%	2.0%	3.4%
	2.0%–5.5%	1.0%–2.8%	1.7%–4.7%
Yes family history ovarian cancer	2.9%	2.7%	3.9%
	1.9%–3.6%	1.8%–3.4%	2.6%–4.9%
Yes/≥1 year talc use	13.0%	12.2%	15.1%
	8.7%–16.8%	8.1%–15.8%	10.0%–19.5%
Three factors (no tubal ligation, no/<1 year oral contraceptives, yes/≥1 year talc use)	50.8% 39.7%–59.5%	51.2% 40.8%–59.3%	47.9% 37.8%–55.8%
All 6 factors	57.9%	56.1%	53.8%
	48.7%–65.3%	46.8%–63.3%	45.0%–60.7%

[a]Using the all race/ethnicity adjusted ORs from Table 3.
[b]The PARs were mutually adjusted for the variables shown in this table as well as for age group (<30, 5-year age groups to age 79), interviewer and study, menopausal status, age at menarche, hormone therapy use, BMI, income, and education.

it was 90.6% in non-Hispanic whites, 83.8% in Hispanics, and 80.5% in African Americans, so that a shift to the low-risk category, that is, having a tubal ligation, will have a substantial impact. In contrast, the PAR% due to nulliparity is lower because being parous is already highly prevalent; 72.2% in non-Hispanic whites, 83.6% in African Americans, and 82.1% in Hispanics, so that a shift to the low-risk category will have a lesser impact on the overall disease burden.

The mean number of births among parous IEOC cases was 2.5 in non-Hispanic whites, 2.8 in African Americans, and 3.1 in Hispanics (Table 2, bottom). We repeated the PAR% calculations after categorizing births as 0, 1, 2, 3, and 4+ using the 4+ category as baseline: The associated PAR% values increased as expected but the relationships of the PAR%s by racial/ethnic group were essentially unaltered. Similarly, we categorized oral contraceptive use in finer categories of <1 year, 1 to 4 years, 5 to 9 years, and 10+ years with little effect on the relationships of the PAR%s by racial/ethnic group (data not shown).

Discussion

With the high mortality and the lack of effective early screening for ovarian cancer, better understanding of preventive risk factors is a priority. The primary motivation for this analysis was to determine whether the six confirmed nongenetic risk factors for IEOC (parity, use of oral contraceptives, tubal ligation, endometriosis, first-degree family history of ovarian cancer, and use of genital talc) in non-Hispanic whites are also risk factors in Hispanics and African Americans. The risk patterns associated with these six factors were comparable in the three racial/ethnic groups (Table 3), and the PAR%s for the factors jointly (Table 4) were also very similar.

An additional objective was to determine whether these six risk factors jointly could explain the 29% and 15% lower incidence of ovarian cancer in African Americans and Hispanics, respectively, compared with non-Hispanic whites. The incidence of ovarian cancer as reported by SEER, and other cancer registries, is calculated by considering all women in the denominator (population at risk) without removing those who have had a bilateral oophorectomy and are not at risk. Thus, estimates of racial/ethnic differences in IEOC based on SEER data can be "improved" by accounting for the racial/ethnic differences in the prevalence of bilateral oophorectomy.

Although Lowder and colleagues (12) in their analysis of oophorectomy rates in women undergoing a hysterectomy in the National Hospital Discharge Survey covering the period 1979 to 2004, found that the proportion was approximately 40% and did not differ by racial/ethnic group; Jamison and colleagues (13) in their analysis of hysterectomy prevalence in women over age 50 in the Behavioral Risk Factor Surveillance System covering the years 1992 to 2008 found that the rate of hysterectomy was clearly higher in African-American women (47%) than in non-Hispanic whites (41%), and lower still in Hispanic women (36%). Using figures from these two studies in Equation A (see Statistical analysis) to adjust incidence rates for the proportion of women with a history of oophorectomy, we estimate that the observed 29% lower incidence rate in African Americans compared with non-Hispanic whites based on SEER data would be adjusted to 27% $[= 1 - 0.71 \times (1 - 0.41 \times 0.4)/(1 - 0.47 \times 0.4)]$. The PAR% of non-Hispanic whites was slightly higher at 57.8% than the PAR% in African Americans at 53.8% (Table 4); taking this into account, by use of Equation B (see Statistical analysis), reduced the difference in incidence between the two groups further from the adjusted 27% to 20%. Overall, taking into account the correction in the population at risk (denominator) and the PAR%, the difference in the African-American to non-Hispanic white incidence rates was reduced by 31% (1%–20%/29%). Given that hysterectomy rates are lower in Hispanics compared with non-Hispanic whites, Hispanics would be at even lower RR than what is observed in SEER; the 15% lower incidence rate in Hispanics compared with non-Hispanic whites would increase to 17% when using the correct at-risk denominator. The PAR% difference will change the difference slightly less in Hispanics compared with non-Hispanic whites from 17% to 13%. When taking into consideration the correct population at risk and the PAR%, the difference in incidence rates between Hispanics and non-Hispanic

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whites is reduced by 13% (1%–13%/15%). Thus, this type of analysis suggests that further investigations are needed to identify other risk factors that may explain the remaining differences in IEOC rates between these three racial/ethnic groups.

Strengths of this study include the ability to evaluate the relative comparability in the effect of several well-established risk factors in non-Hispanics whites, Hispanics, and African Americans. Our results on Hispanics fill a knowledge gap, as this is the first study to examine etiologic risk factors for ovarian cancer in this growing minority population in the United States. Identical questionnaires and protocols were used in these four studies. Although information on these six factors was based on self-report, there is no evidence of systematic misclassification bias as the direction of racial/ethnic differences in the prevalence of tubal ligation, use of oral contraceptives, and endometriosis are consistent with other studies (6, 14–16). However, these results must be considered with caution as we were limited in that the sample sizes of Hispanics and African Americans were modest, and we investigated only the six factors that are confirmed, noncontroversial, showing strong associations with all invasive ovarian cancers in non-Hispanic whites. The modest sample sizes precluded us from conducting analyses separately by histologic type. The response rate for the three racial/ethnic groups was also modest, but not unlike the response rate for other case–control studies on ovarian cancer.

The comparable risk factor associations in IEOC in African Americans, Hispanics, and non-Hispanic whites contrast sharply with the more disparate risk factor patterns in breast cancer by race/ethnicity. A number of factors that are known to affect breast cancer risk in non-Hispanic whites do not appear to influence risk in African Americans and these differences cannot be explained by different prevalence of estrogen receptor/progesterone receptor–positive breast tumors between the two groups (17–21). Breast cancer risk factors also appeared to differ profoundly between Hispanics and non-Hispanic whites in one of the few studies with comparable data on both race/ethnic groups (15). Given the more comparable risk factor patterns in IEOC for non-Hispanic whites, Hispanics, and African Americans, devising strategies to lessen the burden of IEOC will be applicable to all groups.

Summary

Results from these population-based case–control studies suggest that the six well-established risk factors for IEOC accounted for about 60% of ovarian cancer risk in non-Hispanic whites, Hispanics, and African Americans. There were differences in the prevalence of these factors in the different racial/ethnic groups, and the 27% lower incidence of ovarian cancer in African Americans compared with non-Hispanic whites was reduced to 20% when these differences were adjusted for, but adjustment for these differences in prevalence accounted for only a very small amount of the lower incidence rate in Hispanics.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The ideas and opinions expressed herein are those of the authors, and endorsement by the State of California, the California Department of Health Services, the National Cancer Institute, or the Centers for Disease Control and Prevention or their contractors and subcontractors is not intended nor should be inferred.

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Cancer Epidemiology, Biomarkers & Prevention

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African Americans and Hispanics Remain at Lower Risk of Ovarian Cancer Than Non-Hispanic Whites after Considering Nongenetic Risk Factors and Oophorectomy Rates

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Markers of inflammation and risk of ovarian cancer in Los Angeles County

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Factors that increase inflammation have been suggested to influence the development of ovarian cancer, but these factors have not been well studied. To further investigate this question, we studied the role of talc use, history of endometrioisis and use of non-steroidal anti-inflammatory drugs (NSAIDs) and risk of ovarian cancer in a population-based case-control study in Los Angeles County involving 609 women with newly diagnosed epithelial ovarian cancer and 688 population-based control women. Risk of ovarian cancer increased significantly with increasing frequency and duration of talc use; compared to never users risk was highest among long-duration (20+ years), frequent (at least daily) talc users (adjusted relative risk (RR) = 2.08, 95% confidence interval (CI) = 1.34–3.23). A history of physician-diagnosed endometriosis was statistically significantly associated with risk (RR = 1.66, 95% CI = 1.01–2.75). Women who were talc users and had a history of endometriosis showed a 3-fold increased risk (RR = 3.12, 95% CI = 1.36–7.22). Contrary to the hypothesis that risk of ovarian cancer may be reduced by use of NSAIDs; risk increased with increasing frequency (per 7 times/week, RR = 1.27, 95% CI = 1.14–1.43) and years of NSAID use (per 5 years of use, RR = 1.25, 95% CI = 1.10–1.42): this was consistent across types of NSAIDs. We conclude that risk of ovarian cancer is significantly associated with talc use and with a history of endometriosis, as has been found in previous studies. The NSAID finding was unexpected and suggests that factors associated with inflammation are associated with ovarian cancer risk. This result needs confirmation with careful attention to the reasons for NSAID use.
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Key words: talc; endometriosis; non-steroidal anti-inflammatory drugs; ovarian cancer

In 1999, Ness and Cottreau proposed that chronic inflammation may lead to the development of epithelial ovarian cancer.[1] They hypothesized that factors including talc exposure, endometriosis and pelvic inflammatory disease (PID) may increase risk by a common pathway, increasing local inflammation of the "ovarian epithelium." They also suggested that studying the effect of non-steroidal anti-inflammatory drugs (NSAIDs) may offer additional opportunities to evaluate the inflammation hypothesis. In a 2008 paper, Merritt *et al.*[2] studied the role of inflammation, based on histories of talc use, PID, endometriosis and use of NSAIDs in the same study. They concluded that chronic inflammation is unlikely to play an important role because risk of ovarian cancer was modestly increased in association with talc use and history of endometriosis and was unrelated to use of NSAIDs but they restricted attention to medication use in the 5 years prior to diagnosis of ovarian cancer, rather than long-term use.[2] No support for the use of NSAIDs was found in a recent study conducted in Seattle, Washington which collected information on lifetime medication use. These investigators found increased risk of ovarian cancer in association with use of acetaminophen, aspirin and other NSAIDs, particularly among long (10+ years) term users.[3] We have conducted a population-based case-control study of ovarian cancer in Los Angeles County to further investigate the role of inflammation in the risk of ovarian cancer. We focused our attention on risk in relation to lifetime use of talc, NSAIDs and history of various gynecological conditions. We are particularly interested in risk patterns associated with long duration of NSAID use. We report our results herein.

Material and methods

Study design

This was a population-based case-control study of ovarian cancer. Eligible patients were English speaking residents of Los Angeles County between the ages of 18 and 74 inclusive who had histologically confirmed invasive or borderline (low malignant potential; LMP) ovarian cancers that were first diagnosed from 1998 to 2002. The cases were identified by the Cancer Surveillance Program (CSP), part of the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program, covering all residents of Los Angeles County.

A total of 1,097 patients meeting the pathological case definition were identified by the CSP. Of these, 136 patients had died or were too ill to be interviewed by the time we contacted them, 109 patients had moved away from Los Angeles County and could not be interviewed in person or they could not be located and 151 patients declined to be interviewed. Interviews were conducted with 701 ovarian cancer patients of whom 15 were later identified who did not have ovarian cancer and they were excluded from all analyses. Of the 686 ovarian cancer patients interviewed, 77 had a previous cancer (excluding non-melanoma skin cancer) before their diagnosis of ovarian cancer and were excluded from this report because their previous cancer diagnosis and/or treatment may have influenced use of NSAIDs and other risk factors. This left 609 ovarian cancer cases for the present analysis, 81% were invasive tumors [22% localized stage (Stage 1 or 2), 59% advanced stage (Stage 3 or greater) and 19% were LMP tumors. The cell type distribution is as follows: 58% serous, 14% clear cell/endometrioid, 12% mucinous and 16% other category.

Controls were identified through a well-established neighborhood recruitment algorithm, which we have used successfully in previous studies of breast, endometrial and other cancers to investigate the role of hormonal and non-hormonal medications and other factors.[4] For this study, controls were women with at least one intact ovary, with no history of cancer, except possibly non-melanoma skin cancer, and individually matched with patients on race/ethnicity (non-Hispanic White, African-American, Hispanic, Asians) and date of birth (+/−5 years). Neighborhood controls were sought by one of our staff who physically canvassed the neighborhood of the case using a systematic algorithm based on the address of the case. If the first eligible matched control declined to participate, the second eligible matched control in the sequence was asked, and so on. Letters were left when no one was at home, and follow-up by mail, telephone and further visits to the neighborhood continued until either an eligible control agreed to be interviewed or 150 housing units had been screened. When we failed to identify an exact race/ethnicity matched control, we

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accepted a control subject who was matched on age. A total of 688 control women were successfully interviewed by the closing date of the study. The first eligible match was interviewed for 76% of the patients, and the second match for another 17% and the third or later match for 6% of the patients. On average, we contacted a median number of 19 housing units to interview a matched control subjects for those neighborhoods with no refusal, a median of 36 housing units for those neighborhoods with 1 refusal and 58 housing units when there were 2 or more refusals.

Study participants were interviewed using a comprehensive questionnaire that covered medical, gynecological, reproductive and lifestyle history. All but 15 participants were interviewed in-person; cases and their matched controls were interviewed by the same person in almost all instances. A reference date was defined as 2 years before the date of diagnosis of the case. This same reference date was used for each case's matched control subject. Calendars were used to chart major life events and reproductive and contraceptive histories. Specifically, participants were asked if they were ever told by a physician that they had certain gynecological conditions including PID, gonorrhea, endometriosis, ovarian cysts, or uterine fibroids before the reference date. If the response was yes to any of the conditions, participants were then asked the age at which they were first diagnosed with the condition and if they had ever been treated for the condition. To determine the use of talcum powder, participants were asked if they ever used talc at least once per month for 6 months or more. If the response was positive, we then asked whether they had ever used talc in nonperineal areas (feet, arms, chest or back), perineal areas, or on underwear or sanitary pads/diaphragm. Questions on talc use included age at first use, frequency of use (times per month) and years of talc use. Few of the talc users (13 cases, 11 controls) had a tubal ligation or hysterectomy before they started using talc; the numbers were too sparse to determine for certain the effect of talc use in this group and these 24 users were included with the nonusers in subsequent analyses on frequency and duration of talc use. Results were unchanged when we excluded these 24 users from the analysis (data not shown).

We asked the participants whether they took prescription or nonprescription NSAIDs for various conditions including back trouble, arthritis, headaches, migraine headaches, dental problems, sinus trouble, colds or sore throats, menstrual pain or cramps or any other reason. They were also asked if they took any of these medications for prevention reasons, such as for prevention of heart attack. We explicitly asked about usage patterns of 10 common over-the-counter NSAIDs (regular aspirin, buffered aspirin, Anacin, APC, Tylenol, Excedrin, Advil, Nuprin, Coricidin, Dristan), 12 prescription brand-name NSAIDs (Clinoril, Motrin, Anaprox, Feldene, Empirin with codeine, Tylenol with codeine, Darvocet, Indocin, Fiorinal, Percocet-5, Percodan, Naprosyn) and two COX-2 inhibitors (Celebrex, Vioxx). We also asked the participants if they had used any NSAIDs that were not on our list and recorded the drug name and details of use. Respondents were also asked about use of 4 common diuretics; these medications are not hypothesized to be related to ovarian cancer risk, but they were included as a check of differential recall between cases and controls. Taking a specific medication 2 or more times a week for 1 month or longer was categorized as "use"; otherwise participants were considered "non-users." Participants were asked about the ages at first and last use, duration of use, usual frequency of use and the primary reason for such use. All of the medications data were categorized into the following groups based on their components: aspirin, acetaminophen, other NSAIDs, COX-2 inhibitors and diuretics.

Total duration and frequency of the main classes of medication (aspirin, acetaminophen, other NSAIDs) were calculated by summing all use of the same class of medication for each person (there were few users of COX-2 inhibitors, thus results are not shown). We also created a combined variable representing use of all NSAIDs. Duration of use was categorized as no use, less than 5 years, 5–10 years and >10 years of use of the specific type of medication (years of use of different medications may be overlapping). The no use category included never users, occasional users and those who only started to use a particular medication within the interval beginning 2 years before date of diagnosis for case patients and the same reference period for controls to avoid including medication use because of early symptoms in cancer patients. We also repeated the analyses excluding first use of medication within 5 years of diagnosis. In addition, we evaluated effect modification of the NSAIDs-ovarian cancer association by race/ethnicity, education, menopausal status, tumor stage, history of endometriosis, talc use and frequency of Pap smears in the 10 years before reference date.

TABLE I – DEMOGRAPHIC AND OTHER CHARACTERISTICS OF OVARIAN CANCER PATIENTS AND CONTROLS

	Cases $N = 609$	Controls $N = 688$	RR	95% CI[1]
Race/ethnicity				
Non-Hispanic White	381	503		
Black	41	44		
Hispanic	136	103		
Asian	51	38		
Age				
≤34	40	36		
35–44	92	138		
45–54	162	227		
55–64	149	162		
65+	166	125		
Education				
≤high school	92	50		
Some college	109	81		
College graduate	223	242		
Graduate	185	315		
Family history of ovarian cancer				
No	581	672	1.00	
Yes	26	16	1.76	0.89–3.47
p-value			0.10	
Number of livebirth				
0	156	149	1.00	
1	98	110	0.76	0.52–1.12
2	157	202	0.61	0.43–0.86
3	109	118	0.61	0.41–0.90
4+	89	109	0.34	0.22–0.53
p trend			<0.0001	
Oral contraceptives				
0 yr	241	189	1.00	
>0 to <5 yr	259	261	0.98	0.73–1.32
≥5 to <10 yrs	57	112	0.54	0.36–0.82
≥10 yrs	52	126	0.40	0.26–0.61
p trend			<0.0001	
Tubal ligation				
No	531	553	1.00	
Yes	78	135	0.66	0.47–0.93
p value			0.017	

[1]Adjusted for race/ethnicity, age, education, tubal ligation, family history of ovarian cancer, menopausal status, use of oral contraceptives, and parity.

The study was approved by the Institutional Review Board of the Keck School of Medicine at the University of Southern California. Informed consent was obtained from each case and control before her interview.

Statistical methods

We calculated odds ratios as estimates of relative risk (RR), their corresponding 95% confidence intervals (CIs) and statistical significance (p) values. We used conditional stratified logistic regression analysis, with stratification sets defined jointly by age (<35, 35–44, 45–54, 55–64, ≥65) and race/ethnicity (non-Hispanic White, African-American, Hispanic, Asians). All regression models also included as categorical covariates education level (high school or less, some college, college graduate, >college),

TABLE II – MULTIVARIABLE RRS (95% CIS) FOR TALC USE AND RISK OF OVARIAN CANCER

	Cases	Controls	RR	95% CI[1]
Talc use				
No[2]	363	469	1.00	
Yes	242	219	1.48	1.15–1.91
Yes, non-perineal area[3]	112	103	1.43	1.03–1.98
Yes, perineal area	130	116	1.53	1.13–2.09
Frequency and duration of talc use				
No	363	469	1.00	
1 ≤20 yrs and ≤10 times/month	35	31	1.36	0.79–2.32
1 ≤20 yrs and >10 to ≤30 times/month	23	30	1.16	0.63–2.12
1 ≤20 yrs and >30 times/month	21	21	1.23	0.63–2.41
>20 yrs and ≤10 times/month	45	49	1.27	0.80–2.01
>20 yrs and >10 to ≤30 times/month	51	43	1.57	0.99–2.50
>20 yrs and >30 times/month	67	45	2.08	1.34–3.23
p (6 df)				*p* = 0.032
Total times of talc use				
No	363	469	1.00	
≤5200	49	52	1.20	0.77–1.88
>5200 to ≤15600	46	47	1.38	0.87–2.20
>15,600 to ≤52000	63	61	1.34	0.89–2.02
>52000	84	59	1.99	1.34–2.96
p (1 df)				*p* = 0.0004
Total times of talc use				
No	363	469	1.00	
Before 1975				
≤5200	24	35	0.84	0.47–1.51
>5200 to ≤15600	29	29	1.41	0.79–2.53
>15,600 to ≤52000	49	45	1.45	0.91–2.31
>52000	82	58	1.93	1.29–2.88
After 1975				
≤5200	25	17	1.95	0.98–3.89
>5200 to ≤15600	17	18	1.17	0.56–2.48
>15,600	16	17	0.98	0.45–2.13

[1]Adjusted for race/ethnicity, age, education, tubal ligation, family history of breast/ovarian cancer, menopausal status, use of oral contraceptives and parity.–[2]Subjects (13 Cases, 11 Controls) reported tubal ligation and/or hysterectomy before started talc use and were included with the never users.–[3]Included arms and extremities.

age at menarche (<=11, 12, 13, 14+), parity (0, 1, 2, 3, 4+ births), use of oral contraceptives (none, >0 to <5, 5 to <10, 10+ years), family history of breast/ovarian cancer (no/yes), menopausal status (premenopausal, natural or surgical menopause) and tubal ligation (no/yes). Results obtained using stratified conditional logistic regression methods were consistent with those obtained in matched analyses that preserved the original case-control matching, and we show the results from the stratified analyses. All statistical significance *p* values quoted are two-sided and are standard chi-squared tests based on differences in log-likelihoods.

Results

The race/ethnicity, age and education of the ovarian cancer cases and controls are shown in Table I. Risk of ovarian cancer increased in association with family history of ovarian cancer (RR = 1.76, 95% CI = 0.89–3.47) and decreased significantly with increasing number of births (RR per birth = 0.79, 95% CI = 0.72–0.88), with increasing duration of oral contraceptive use (RR per 5 years of use = 0.73, 95% CI = 0.64–0.83) and with a history of tubal ligation (RR = 0.66, 95% CI = 0.47–0.93).

Table II shows risk associations with talc use. Ever use of talc was associated with a statistically significant increased risk (RR = 1.48, 95% CI = 1.15–1.91). This included talc that was applied to the perineal area (RR = 1.53, 95% CI = 1.13–2.09) and to the nonperineal area only (RR = 1.43, 95% CI = 1.03–1.98). Elevated risks were found among those who used talc on sanitary napkins (RR = 1.61, 95% CI = 0.93–2.78), underwear (RR = 1.71, 95% CI = 0.99–2.97) and on diaphragm/cervical caps (RR = 1.14, 95% CI = 0.46–2.87). When we examined risk patterns by frequency and duration of talc use, the effect of frequency of use was relatively modest among users of less than 20 years but there was a clear trend of increasing risk with increasing frequency of use among longer duration (>20 years) users. Compared with never users, risk was highest in long-term (>20 years), daily (>30 times/month) talc users (RR = 2.08, 95% CI = 1.34–3.23). Risk increased significantly with lifetime total times of talc use, but the association was limited to those who started talc use before 1975 (p_{trend} <0.001). The association between talc use and risk of ovarian cancer was strongest for serous ovarian cancer, the RR associated with any use was 1.70 (95% CI = 1.27–2.28). The risk associations for talc use and other histologic cell types overlapped with the finding for serous ovarian cancer (RRs were 0.99 for mucinous, 1.19 for clear/endometrioid and 1.46 for other cell types). Elevated risks in relation to talc use were found for those with invasive cancers (RR = 1.31, 95% CI = 0.85–2.01 for localized stage; RR = 1.66, 95% CI = 1.22–2.26 for advanced stage) and LMP tumors (RR = 1.32, 95% CI = 0.88–2.22).

Women with a history of physician-diagnosed endometriosis experienced a nearly 2-fold increased risk of ovarian cancer (RR = 1.95, 95% CI = 1.20–3.17). The risk associated with endometriosis remained statistically significant after adjustment for other gynecological conditions including PID, gonorrhea, ovarian cysts and uterine fibroids (adjusted RR = 1.66, 95% CI = 1.01–2.75) (Table III). Small (4–18%) increased risks were also associated with a history of the other gynecological conditions as mentioned earlier but none of these findings were statistically significant (data not shown). The risk of ovarian cancer increased significantly (RR = 2.58) for more recent diagnoses of endometriosis (2–10 years prior to cancer diagnosis) and was less strong (RR = 1.58) for women with diagnosis more than 10 years previously. The endometriosis-risk association was stronger for invasive cancers (RR = 1.80, 95% CI = 0.85–3.80 for localized stage, RR =

TABLE III – MULTIVARIABLE RRS (95% CIS) FOR PREVIOUS OVARIAN DISEASE AND RISK OF OVARIAN CANCER

		Cases	Controls	Adjusted RR[1]	Adjusted RR[2]
Pelvic inflammatory disease					
No		579	657	1.00	1.00
Yes		25	22	1.48 (0.78–2.82)	1.15 (0.60–2.21)
Gonorrhea					
No		553	619	1.00	1.00
Yes		51	60	1.19 (0.77–1.84)	1.04 (0.67–1.62)
Endometriosis					
No		553	642	1.00	1.00
Yes		51	37	1.95 (1.20–3.17)	1.66 (1.01–2.75)
Years since first diagnosed					
2–10		15	8	2.66 (1.06–6.64)	2.58 (1.03–6.48)
11+		36	29	1.56 (0.90–2.70)	1.58 (0.91–2.76)
Talc	Endometriosis				
No	No	332	435	1.00	1.00
No	Yes	29	28	1.68 (0.93–3.04)	1.67 (0.92–3.01)
Yes	No	221	207	1.50 (1.15–1.94)	1.49 (1.15–1.94)
Yes	Yes	22	9	3.17 (1.38–7.29)	3.12 (1.36–7.22)
p (3df)					0.001

[1]Adjusted for race/ethnicity, age, education, tubal ligation, family history of breast/ovarian cancer, menopausal status, use of oral contraceptives and parity.–[2]Adjusted for other conditions including pelvic inflammatory diseases, gonorrhea, endometriosis, ovarian cyst and fibroids.

1.87, 95% CI = 1.04–3.35 for advanced stage) than for LMP tumors (RR = 1.28, 95% CI = 0.56–2.95). Although the point risk estimate was slightly higher for clear/endometrioid cancers (RR = 1.97), the risk associations for the other cell types were all around 1.70. Compared with women who did not have endometriosis and were nontalc users, risk increased 3-fold (RR = 3.12, 95% CI = 1.36–7.22) in women who had endometriosis and were talc users whereas about 50% increased risk was observed in women who had either exposure.

Risk of ovarian cancer increased significantly with increasing duration and frequency of use of all NSAIDs (*i.e.*, aspirin, acetaminophen, other NSAIDs). The risk per 5 years of NSAID use was 1.25 (95% CI = 1.10–1.42) and the risk per 7 times of NSAID use per week was 1.27 (95% CI = 1.14–1.43). The effect of total pill use was essentially identical to the effect of frequency of use. This pattern of risk elevation was found for aspirin, acetaminophen and other NSAIDs although the results were statistically significant only for other NSAIDs (Table IV). Risks patterns remained essentially unchanged when we adjusted for indication of use (*i.e.*, headaches, back pain, menstrual pain and others) or history of endometriosis and other gynecological conditions. Risk associations were only slightly reduced when we restricted our analyses to medication use at least 5 years before diagnosis; the RR per 5 years of all NSAID use was 1.20 (95% CI = 1.06–1.43) and the risk per 7 times of NSAID use per week was 1.23 (95% CI = 1.09–1.38). In contrast, risk of ovarian cancer was not significantly related to duration or frequency of use of diuretics (RRs were 1.00, 1.39, 0.89, 0.65, respectively for no, 1–5, >5–10, >10 years of use, p_{trend} = 0.50).

Table V presents stratified results, when we performed a series of analyses to evaluate whether the findings with NSAID use were consistent across levels of various subgroups of interest including race/ethnicity, education, menopausal status, tumor stage, endometriosis, talc use, use of oral contraceptives, parity and frequency of Pap smears in recent 10 years as a marker of access to care. Elevated risks in relation to NSAID use were found in all the subgroup analyses; findings were similar by race/ethnicity, menopausal status, talc use, oral contraceptive use, parity and history of Pap smear. There were some differences in risk estimates by education, tumor stage, history of endometriosis but they were not statistically significantly different. We considered these differences by tumor stage, history of endometriosis and education in our interpretation of these results.

Discussion

The main objective of this population-based case-control study was to comprehensively investigate the role of inflammation in risk of ovarian cancer by studying factors that have been hypothesized to increase inflammation (*e.g.*, talc, endometriosis) or to reduce inflammation (NSAIDs) simultaneously in the same population. Our findings on talc and endometriosis are consistent with previous findings and are compatible with the hypothesis that these factors increase the risk of ovarian cancer and that inflammation may be a common pathway.[1,2,5] However, contrary to the study hypothesis that NSAIDs may have chemopreventive effects by decreasing inflammation,[6] we found that risk of ovarian cancer increased significantly with increasing frequency and duration of NSAIDs use.

Our results on NSAID and risk are similar to the recent results reported in the population-based case-control study conducted in Seattle, Washington.[3] In both studies, women were asked to recall prescription and nonprescription medications taken over their lifetime for various conditions. In the Seattle study, risk of ovarian cancer increased significantly in association with 10+ years of use of acetaminophen (RR = 1.8, 95% CI = 1.3–2.6), aspirin (RR = 1.6, 95% CI = 1.1–2.2) and other NSAIDs (RR = 1.3, 95% CI = 1.0–1.7).[3] Mechanisms whereby use of NSAID may increase risk of ovarian cancer may be related, in part, to the underlying conditions associated with medication use.

However, our results and those from the Seattle study differed from most previous studies on this topic. As Cramer *et al.* reported risk reduction of ovarian cancer with ever use of aspirin, and acetaminophen, but not with use of ibuprofen,[7] 7 (3 case-control, 4 cohort) of 13 (7 case-control, 6 cohort) studies have found no significant relation with use of NSAID. The case-control studies showing null findings were conducted in Italy,[8] the UK[9] and Australia,[2] and they investigated risk associations with use of aspirin,[8] acetaminophen and other NSAID,[9] and aspirin and other NSAIDs,[2] respectively. There was also no relationship between acetaminophen use and risk in the Cancer Prevention II Mortality Study[10] or between risk and use of low-dose aspirin[11] and other NSAIDs[12] in a Danish prescription database study. In the Breast Cancer Detection Demonstration Project Follow-up Study (BCDDP), risk was not significantly related to use of aspirin, acetaminophen and other NSAIDs but risk was increased with 5+ years of other NSAID use (RR = 2.0, 95% CI = 0.95–4.2).[13] Six other studies (4 case-control, 2 cohort) are supportive of an inverse

TABLE IV – MULTIVARIABLE RRS[1] (95% CIS) FOR USE OF ALL NSAIDs (ASPIRIN, ACETAMINOPHEN, OTHER NSAIDs) AND RISK OF OVARIAN CANCER

	Excluded medication use the 2 years before reference date		
	Cases	Controls	RR (95% CI)
All NSAIDs			
Years of use			
Never[2]	355	486	1.00
1 to 5 yr	117	99	1.71 (1.23–2.39)
>5 to ≤10 yr	37	33	1.59 (0.93–2.72)
>10 yr	79	57	1.81 (1.21–2.71)
p trend			<0.001
No. of pills per week			
Never[2]	355	486	1.00
1 to ≤7/wk	82	66	1.62 (1.11–2.39)
>7 to ≤14/wk	41	49	1.09 (0.67–1.78)
>14/wk	110	74	2.24 (1.56–3.21)
p trend			<0.001
Total no. of pills			
Never	355	486	1.00
1 to ≤1096	73	63	1.60 (1.08–2.38)
>1096 to 6428	73	66	1.43 (0.96–2.13)
>6428	87	60	2.22 (1.49–3.31)
p trend			<0.001
Years of use by type[3]			
Aspirin			
Never[2]	492	597	1.00
1 to 5 yr	46	25	2.13 (1.21–3.77)
>5 to ≤10 yr	13	18	0.70 (0.31–1.58)
>10 yr	31	28	1.15 (0.62–2.13)
p trend			0.43
Acetaminophen			
Never[2]	491	590	1.00
1 to 5 yr	47	53	0.87 (0.53–1.41)
>5 yr	44	25	1.71 (0.94–3.09)
p trend			0.12
Other NSAIDs			
Never[2]	450	575	1.00
1 to 5 yr	87	61	1.76 (1.18–2.63)
>5 to ≤10 yr	17	19	1.18 (0.55–2.53)
>10 yr	28	13	2.18 (1.03–4.63)
p trend			0.008
Frequency of use by type[3]			
Aspirin			
Never[2]	492	597	1.00
1 to ≤7/wk	61	48	1.49 (0.94–2.35)
>7	29	23	1.18 (0.61–2.29)
p trend			0.21
Acetaminophen			
Never[2]	491	590	1.00
1 to ≤7/wk	48	45	1.04 (0.63–1.71)
>7 /wk	43	33	1.36 (0.78–2.36)
p trend			0.33
Other NSAIDs			
Never[2]	450	575	1.00
1 to ≤7/wk	52	38	1.56 (0.95–2.56)
>7 to ≤14/wk	29	25	1.27 (0.68–2.40)
>14/wk	51	30	2.22 (1.30–3.79)
p trend			0.0009

[1]Adjusted for age, education, race, tubal ligation, family history of breast/ovarian cancer, menopausal status, use of oral contraceptives, parity and talc use.–[2]Included participants who started medication within 2 years of diagnosis/reference date.–[3]Additional adjustment for history of PID, gonorrhea, ovarian cysts, endometriosis, and fibroids. The RRs for aspirin, acetaminophen and other NSAIDs were mutually adjusted. Aspirin included regular aspirin, buffered aspirin; acetaminophen included Tylenol, coricidin, Dristan, darvocet, Percocet, Excedrin; other NSAID included advil, nurin, clinoril, motrin, anaprox, feldene, indocin, naprosyn.

association with NSAIDs use, one reported significant risk reduction with acetaminophen use[14] while 4 studies found significant reduced risk with use of other NSAIDs[15–18] but there were differences in these results. In one study, an inverse association was found only in nulliparous and nonoral contraceptive users.[18] No dose-response relationship was observed in a second study,[15] and information on NSAID use was limited to the 5 years before diagnosis in a third study.[17] Aspirin use was not significantly associated with risk in these 5 studies.[14–17,19] Ascertainment of NSAID use was heterogeneous in these studies: different NSAIDs were included, the exposure period varied (*e.g.*, adult use, use in previous 20 years or previous 5 years before ovarian cancer diagnosis), and information on frequency and duration of NSAID use was asked in only some studies.

An advantage of our study is that we collected detailed information on adult usage history of both over the counter and prescription NSAIDs including duration and frequency of use and indication for use. Our results suggest increased risk associated with duration and frequency of use of aspirin, acetaminophen and other NSAIDs although only the findings for other NSAIDs were statistically significant on their own. We adjusted for potential confounders and indication for use; the latter was considered in only some previous studies. Nevertheless, our results should be interpreted with caution for the following reasons. Our assessment of NSAID use was based on self-report without assessment of reliability of recall. However, a drug validation study conducted by colleagues in Los Angeles County found high and comparable concordance rate of recall of analgesics in cancer patients and control subjects.[20] Regular NSAID use was reported by 29% (31% in non-Hispanic whites) of controls in our study; comparable with the rate reported in Wisconsin and Massachusetts (34%)[18] but lower than that in Seattle (41%).[3] Differences in the assessment of use of NSAID complicate comparison of prevalences of use between studies.

Although an increased risk was specific to NSAIDs use and no increased risk was found with diuretic use, we cannot rule out the possibility of selective recall bias among ovarian cancer cases. Given that many NSAIDs products are available and use may be episodic, it is conceivable that some cases may be more motivated to remember their NSAID use than control subjects. There is also the possibility of surveillance bias and that certain health conditions led to regular NSAID use, resulting in frequent doctor visits, which increased the chances of ovarian cancer detection. As noted earlier, the prevalence of NSAID use was higher in women with LMP tumors or localized cancer than those with advanced stage cancers, and the magnitude of association was stronger for earlier stage cancers. However, the proportion of LMP/localized stage cancers among those we interviewed (41%) and those we failed to interview (39%) was not dissimilar, suggesting there should be minimal overestimation of the overall effect of NSAID in relation to this reason. There also may be residual confounding by indication for use. Another possible explanation for our observed positive finding is that women with early symptoms of undiagnosed ovarian cancer take pain medications to relieve these symptoms. This seems less likely because our results were essentially unchanged when we excluded participants who first started using these medications within the 5 years of diagnosis. Finally, we consider possibly that selection bias of cases and controls may have affected our finding. Our response rate was modest; cases who participated may differ from those who did not participate. Although controls in our study had more years of education than cases, there was no consistent pattern in the NSAID-risk association by education. The NSAID-risk association was most apparent in women who were college graduates but was very similar in women with high school education or less and those who had more than college education. Thus, despite these limitations, our results raise the concern that NSAIDs, taken as aspirin, acetaminophen or other NSAIDs, may actually increase the risk of ovarian cancer.

In our study, history of self-reported history of endometriosis that was diagnosed by a physician was associated with a significant 66% increased risk of ovarian cancer. Given that the elevated risk was observed for those with previous endometriosis for at least 11+ years, it is unlikely that our finding is due to detection bias but suggests that endometriosis may have an etiological role.

TABLE V – PREVALENCE OF NSAID USE IN CASES AND CONTROLS AND RRS (95% CI)[1] PER 5 YEARS OF NSAID USE

		ever NSAID-cases (%)	ever NSAID-controls (%)	10+ yrs of NSAIDs-cases (%)	10+ yrs of NSAID-controls	RR (95% CI) per 5 years of NSAID
Race/ethnicity	Non-Hipsanic Whites	45%	31%	17%	10%	1.23 (1.07–1.42)
	Other	31%	19%	7%	4%	1.37 (1.03–1.84)
Education	<College	36%	29%	14%	10%	1.09 (0.84–1.41)
	College graduate	48%	27%	16%	7%	1.71 (1.36–2.15)
	Graduate	33%	28%	11%	9%	1.05 (0.85–1.30)
Menopause	Premenopause	34%	22%	7%	5%	1.35 (1.05–1.73)
	Postmenopause	43%	34%	17%	11%	1.22 (1.06–1.42)
Tumor stage	LMP	47%	28%	14%	8%	1.37 (1.11–1.69)
	Invasive, Stage 1 or 2	40%	28%	14%	8%	1.36 (1.11–1.67)
	Invasive, Stage ≥3	37%	28%	13%	8%	1.16 (1.01–1.35)
Endometriosis	No	39%	27%	12%	9%	1.23 (1.08–1.40)
	Yes	50%	44%	26%	8%	1.52 (0.96–2.43)
Talc	No	36%	25%	13%	6%	1.31 (1.10–1.55)
	Yes	45%	35%	15%	14%	1.14 (0.94–1.38)
Oral Contraceptives	No	35%	25%	13%	10%	1.10 (0.89–1.37)
	Yes	43%	29%	14%	8%	1.31 (1.12–1.53)
Parity	No	41%	31%	15%	9%	1.28 (0.98–1.68)
	Yes	40%	27%	13%	8%	1.25 (1.09–1.45)
Pap smear[2]	≤5 times	34%	24%	11%	7%	1.22 (0.94–1.59)
	>5 times	42%	30%	15%	9%	1.27 (1.09–1.47)

[1]Adjusted for age, education, race, tubal ligation, family history of breast/ovarian cancer, menopausal status, use of oral contraceptives and parity.–[2]Frequency of Pap smears in the 10 years before reference date.

No association between endometriosis and ovarian cancer was reported in the Iowa Women's Health Study, but this may be because of the relatively limited number of ovarian cancers in this cohort and the low prevalence of endometriosis (~3%).[21] Endometriosis was associated with about a 30% increased risk in an Australian population-based case-control study[2] and in a pooled analysis of 2,098 cases and 2,953 controls from 4 US population-based case-control studies.[22] Although the prevalences of endometriosis among cases (8.4%) and controls (5.4%) in our study are very comparable with the figures reported in cases (8%) and controls (6%) in previous case-control studies,[2,22] a limitation of our study and other case-control studies on this topic is that history of endometriosis is not validated. We did not see meaningful differences in history of endometriosis by cell type (11% for endometrioid/clear cell *vs.* 8% for other cell types) of ovarian cancer while a higher prevalence of endometriosis in women with endometroid/clear cell has been usually reported in other studies.[2,23] Interestingly, when one of us (CT) reviewed the pathology reports of the 52 ovarian cancer patients who reported a history of endometriosis, endometriosis in the ovary was documented in only 15 patients (15 of 604 cases = 2.5%) but the percent was higher in women with clear cell/endometrioid (7 of 84 = 8.3%) ovarian cancer compared with the other cell types (8 of 520 = 2.3%). Additional information on the type of endometriosis and location of endometriosis would be helpful in future studies.

The role of talc in the development of ovarian cancer has been studied extensively. In a 2006 review by the International Agency for Research on Cancer (IARC), talc was classified as possibly carcinogenic to humans (*i.e.*, Group 2B) on the basis that most of the 20 epidemiological studies on talc and ovarian cancer show consistently a 30–60% increased risk associated with talc use.[24] However, only about half of the studies examined exposure-response relationships and the evidence for this is less consistent. Our study adds to the small group of studies that have investigated the combination of frequency and duration of talc use on ovarian cancer risk.[25–28] Our results show a significant trend with increasing number of total applications. Using a combined index of total applications or cumulative lifetime days of talc use, 2 studies showed a higher risk with greater exposure[27,29] but this was not observed in 2 other studies.[25,28] When we investigated the combined effect of frequency and duration, our results suggest that the effect of increasing frequency was modest in users of less than 20 years but that the effect of frequency was clearer in women who had used talc for 20 years or more. Our results also suggest that talc use prior to 1976 may be more important. In 1976, talcum powder manufacturers instituted voluntary guidelines to prevent asbestos contamination in talc products and thus formulations after 1976 may be less likely to be contaminated with asbestos fibers. Stronger associations with talc use in the 1960s and 1970s have been reported in some studies[25,27] but not in others.[2,28] Thus, lack of sufficient information on frequency, duration and calendar period of talc use may have contributed to misclassification of this exposure variable in some previous studies.

Our findings on talc use and endometriosis and ovarian cancer risk are compatible with previous studies. However, the NSAID finding in this study was unexpected and requires confirmation with further characterization of the association by frequency and duration of use, cumulative dose and timing of exposure. In addition, it will be important to evaluate the underlying conditions for medication use.

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Cancer Prevention Research

Research Article

Genital Powder Use and Risk of Ovarian Cancer: A Pooled Analysis of 8,525 Cases and 9,859 Controls

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Abstract

Genital powder use has been associated with risk of epithelial ovarian cancer in some, but not all, epidemiologic investigations, possibly reflecting the carcinogenic effects of talc particles found in most of these products. Whether risk increases with number of genital powder applications and for all histologic types of ovarian cancer also remains uncertain. Therefore, we estimated the association between self-reported genital powder use and epithelial ovarian cancer risk in eight population-based case–control studies. Individual data from each study were collected and harmonized. Lifetime number of genital powder applications was estimated from duration and frequency of use. Pooled ORs were calculated using conditional logistic regression matched on study and age and adjusted for potential confounders. Subtype-specific risks were estimated according to tumor behavior and histology. 8,525 cases and 9,859 controls were included in the analyses. Genital powder use was associated with a modest increased risk of epithelial ovarian cancer [OR, 1.24; 95% confidence interval (CI), 1.15–1.33] relative to women who never used powder. Risk was elevated for invasive serous (OR, 1.20; 95% CI, 1.09–1.32), endometrioid (OR, 1.22; 95% CI, 1.04–1.43), and clear cell (OR, 1.24; 95% CI, 1.01–1.52) tumors, and for borderline serous tumors (OR, 1.46; 95% CI, 1.24–1.72). Among genital powder users, we observed no significant trend ($P = 0.17$) in risk with increasing number of lifetime applications (assessed in quartiles). We noted no increase in risk among women who only reported nongenital powder use. In summary, genital powder use is a modifiable exposure associated with small-to-moderate increases in risk of most histologic subtypes of epithelial ovarian cancer. *Cancer Prev Res; 6(8); 811–21. ©2013 AACR.*

Introduction

Powders that are commonly applied either directly to the genital, perineal, or rectal area after bathing or indirectly to underwear, sanitary napkins, tampons, or stored contraceptive devices may contain talc because of its softness, absorbency, and lack of clumpiness (1). However, the presence of talc in commercially available powder formulations has varied over time, even within particular brands of products, limiting the ability of most epidemiologic studies to measure genital talc exposure accurately. Despite this, genital powder use, but not use on other parts of the body, has been linked to increased risk of ovarian cancer, suggesting that powder particles ascending the genital tract may predispose to ovarian cancer development (2–4). Meta-analyses of

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observational studies show 33% to 35% increased risk of ovarian cancer among women who have used genital powders (1, 4, 5), but evidence for a dose–response relationship has been inconsistent. Although dose-response was not addressed in previous meta-analyses (1, 4, 5), some individual studies have reported significant dose-response (4, 6–10) while others have not (9, 11–15).

Epidemiologic and biologic studies show differences in risk-factor profiles and molecular characteristics between ovarian cancer subtypes defined by histology (serous, endometrioid, mucinous, and clear cell) and behavior (borderline and invasive; refs. 16 and 17). For instance, serous tumors are characterized by p53 mutations, whereas mucinous tumors have a high prevalence of KRAS mutations (17) and are not generally associated with reproductive risk factors (16, 18). Because most early studies of powder use and ovarian cancer did not include analysis by histologic subgroups (3, 6, 11, 19–21), histology-specific estimates were not available from these studies for meta-analysis. Most (2, 4, 8, 9, 22), but not all (10, 14, 15, 23), epidemiologic studies of genital powder use and risk of ovarian cancer that have evaluated histologic subgroups have found the association to be strongest for serous-invasive tumors. Such tumors comprise the most common variety of ovarian cancer and few previous studies have had sufficient statistical power to evaluate the association between genital powder use and risk of other histologic subtypes. In the present study, we evaluated associations between genital powder use and risk of ovarian cancer overall, by invasiveness and by histologic type in a pooled analysis of eight population-based case–control studies with relevant data from the Ovarian Cancer Association Consortium (OCAC), a consortium founded in 2005 to validate promising genetic associations in epidemiologic studies of ovarian cancer.

Materials and Methods

Participating studies

Studies participating in the OCAC consortium as of April 2010 that collected data on powder use were included. Each study was approved by an institutional ethics committee and all participants provided informed consent. Detailed description of the OCAC consortium is available elsewhere (24). Characteristics of the eight case–control studies contributing data to this analysis are presented in Table 1. Six studies were conducted in the United States [Diseases of the Ovary and their Evaluation Study (DOV; ref. 14), Hawaii Ovarian Cancer Study (HAW; ref. 25), Hormones and Ovarian Cancer Prediction Study (HOP; ref. 26), North Carolina Ovarian Cancer Study (NCO; ref. 27), New England Case–Control Study of Ovarian Cancer (NEC; ref. 4), and University of Southern California Study of Lifestyle and Women's Health (USC; ref. 28)], one study in Australia [Australian Cancer Study (AUS; ref. 7)], and one study in Canada [Southern Ontario Ovarian Cancer Study (SON; ref. 15)]. Overall, our analyses included 8,525 cases of ovarian, fallopian tube, or peritoneal cancer and 9,859 controls. Five studies previously reported on powder use [AUS (7), DOV (14), NCO (27), NEC (4), and SON (15)], three of which provided data for this analysis that had not been included in their previous powder-related publication (DOV, NEC, and AUS). The remaining three studies have not previously published their genital powder use data (HAW, HOP, and USC).

Exposure and covariate data

Data collected from participants about genital powder use varied between studies. Harmonized analytic exposure variables were developed by comparing questionnaires between the eight participating studies. The majority of the studies have obtained information on duration and frequency of powder use, age at first powder use, use by sexual partners, and non-genital use (Table 1). We defined genital powder use as any type of powder (talc, baby, deodorizing, cornstarch, or unspecified/unknown) applied directly or indirectly (by application to sanitary pads, tampons, or underwear) to the genital, perineal, or rectal area. Because study-specific powder questions included varying degrees of detail about type and method of application, genital powder definitions differ between studies. Criteria for regular genital powder use varied between studies from "ever use" (AUS) to "one year or longer" (DOV); the specific wording for this question is provided in Table 1. Use of body powders on sites other than the genital area was defined as non-genital powder use. Women who reported both genital and non-genital powder use were classified as genital users. Two studies (DOV and SON) did not collect data on nongenital use, and therefore women assigned to "no powder use" for these studies could have a history of non-genital powder exposure. Extensive information on known and suspected risk factors for ovarian cancer was collected in each study, including oral contraceptive use, parity, tubal ligation history, body mass index (BMI), race, and ethnicity.

Statistical analysis

Participants missing case/control status ($n = 17$) or tumor histology ($n = 19$) were excluded from the analysis. We also excluded 1,119 participants who answered "do not know" or were missing data on genital powder use; most of these were from the NCO study, which did not include genital powder questions for the first 720 participants. Furthermore, we excluded participants missing tubal ligation ($n = 55$), oral contraceptive duration ($n = 100$), parity ($n = 3$), or height or weight (BMI; $n = 179$). To examine differences in characteristics between cases and controls, we evaluated two-sample t statistics (age and BMI) and χ^2 statistics (oral contraceptive use, nulliparity, tubal ligation, race/ethnicity, and powder use).

Study-specific ORs and 95% confidence intervals (CI) were estimated using unconditional logistic regression and were summarized by forest plots, including study heterogeneity based on Cochran's Q statistic. As no significant heterogeneity was observed between studies, we calculated pooled ORs and 95% CIs across the studies using conditional logistic regression matched on 5-year age groups and

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Table 1. Characteristics of eight studies included in the analysis of genital powder use and ovarian cancer

				Histology[b]				Behavior[c]		
Study[a]	Diagnosis years	Controls	Cases	Serous	Mucinous	Endometrioid	Clear cell	Invasive	Borderline	Question used to define genital powder use
AUS[g]	2002–2006	1,449	1,432	889 (62%)	174 (12%)	132 (9%)	78 (5%)	1,158 (81%)	274 (19%)	Have you ever used any sort of powder or talc on your genital area, in your underwear or on a sanitary pad or diaphragm?
DOV[g]	2002–2009	1,841	1,565	905 (58%)	186 (12%)	201 (13%)	87 (6%)	1,153 (74%)	412 (26%)	Before (reference date) did you ever use any of the following products routinely during 1 month or more? Powder on sanitary napkins or pads? Vaginal deodorant spray? Before (reference date) did you usually apply any powder to your genital (perineal) area after bathing? We are only interested in times when you did this for at least 1 year or longer.[d]
HAW	1993–2008	755	481	222 (46%)	87 (18%)	69 (14%)	47 (10%)	392 (82%)	89 (19%)	Before (month/year of diagnosis[e]) did you ever use talc, baby, or deodorizing powder dusted or sprayed on your body? By regularly I mean at least once a month for 6 months or more. Did you ever use talc, baby, or deodorizing powder as a dusting powder to the genital or rectal area? As a dusting powder to sanitary napkins? As a dusting powder to underwear? On a diaphragm or cervical cap?
HOP	2003–2008	1,489	735	433 (59%)	53 (7%)	75 (10%)	47 (6%)	568 (88%)	80 (12%)	As an adult and before (reference month/year) did you ever use talc or baby powder or deodorizing powder with talc at least once a month for 6 months or more in any of the following ways: as a dusting powder or deodorizing spray to your genital or rectal areas? On your sanitary napkin? On your underwear? On your diaphragm or cervical cap?
NCO[g]	1999–2008	650	786	489 (62%)	71 (9%)	100 (13%)	65 (8%)	636 (81%)	148 (19%)	Did you ever regularly use cornstarch, talc, baby, or deodorizing powders (dusted or sprayed) at least 1 time per month for at least 6 months? If yes, please tell me if you used cornstarch, talc, baby, or deodorizing powders in any of the following ways: directly to your genital or rectal areas? Applied to your sanitary napkins or tampons? Applied to birth control devices such as cervical cap or diaphragm? Applied to your underwear?

(Continued on the following page)

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Table 1. Characteristics of eight studies included in the analysis of genital powder use and ovarian cancer (Cont'd)

				Histology[b]				Behavior[c]		
Study[a]	Diagnosis years	Controls	Cases	Serous	Mucinous	Endometrioid	Clear cell	Invasive	Borderline	Question used to define genital powder use
NEC[g]	1992–2008	2,329	2,305	1,234 (54%)	281 (12%)	352 (15%)	276 (12%)	1,659 (77%)	486 (23%)	Did you ever regularly use powder on your body or your underwear (at least once per month for any amount of time)? If yes, did you apply powder directly to your genital or rectal areas? To your sanitary napkins or tampons? To your underwear?[f]
SON[g]	1989–1992	564	449	254 (57%)	80 (18%)	71 (16%)	29 (6%)	365 (81%)	84 (19%)	Have you ever used sanitary napkins/tampons? If yes, could you tell me over what ages you have used them, for how many years, what percentage of periods you have used them for, the usual number you have used for each period, whether they were deodorant pads/tampons, and if you used talcum powder or starch on them? Have you ever regulary used talcum powder or starch on your vaginal area after showering or bathing?
USC	1993–1997	782	772	396 (52%)	131 (17%)	75 (10%)	32 (4%)	549 (73%)	205 (27%)	Before (reference month/year), did you ever regularly use talc, baby, or deodorizing powder dusted or sprayed on your body? By regularly I mean at least once a month for 6 months or more. Did you ever use talc, baby, or deodorizing powder as a dusting powder to the genital or rectal area? As a dusting powder to sanitary napkins? As a dusting powder to underwear? On a diaphragm or cervical cap?

[a]AUS, Australian Cancer Study; DOV, Diseases of the Ovary and their Evaluation Study; HAW, Hawaii Ovarian Cancer Study; HOP, Hormones and Ovarian Cancer Prediction Study; NCO, North Carolina Ovarian Cancer Study; NEC, New England Case Control Study; SON, Southern Ontario Ovarian Cancer Study; and USC, University of Southern California Study of Lifestyle and Women's Health.

[b]Cases listed by histology do not sum because mixed, other, undifferentiated, and unknown are not included.

[c]Cases listed by behavior do not sum to the total number of cases because 267 cases are missing behavior information.

[d]In a separate series of questions, participants were asked about powder use with diaphragm storage. Duration was calculated from ages of use. Information on duration, frequency, and timing of use was only collected on genital/perinal powder use after bathing.

[e]Controls were asked "Have you ever regularly used…"

[f]NEC question varied slightly between the three study phases. Between 1992 and 1997 participants were asked, "As an adult and before (reference month/year), did you regularly use talc, baby, or deodorizing powders dusted or sprayed to your body in any of the following ways:". Between 1998 and 2003, women were asked "Did you regularly apply cornstartch, talc, baby, or deodorizing body powder at least one time per month for 6 months or longer? If yes, please tell me if you regularly applied cornstarch, talc, baby or deodorizing body powders in any of the following ways:" Between 2003 and 2008 participants were asked the question listed above.

[g]These studies previously published on genital powder use and ovarian cancer risk. AUS, DOV, and NEC provided new data to the pooled analyses presented here that were not included in previous publications.

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study. All analyses were adjusted for potential confounders: age (continuous), duration of oral contraceptive use (never use, use <2, 2–<5, 5–<10, or ≥10 years), parity (0, 1, 2, 3, or ≥4 children), tubal ligation history, BMI (quartiles based on distribution in controls), and race/ethnicity (non-Hispanic White, Hispanic White, Black, Asian, or other). Family history of breast or ovarian cancer was also considered as covariate but was not included in the final model.

Subtype-specific estimates were calculated for subgroups of ovarian cancer defined by behavior (invasive and borderline) and histology (serous, mucinous, endometrioid, and clear cell) by comparing each case group with all controls. As borderline endometrioid and clear cell tumors are rare, we did not have sufficient numbers to evaluate those types separately.

To measure cumulative dose of genital powder use, we estimated lifetime number of powder applications by multiplying total months of use by frequency of use per month, for all direct and indirect genital powder applications. Women who reported multiple types of genital powder exposure (on underwear, on sanitary napkins or pads, or directly to genital area) during the same time period were assigned the number of genital powder applications equal to the most commonly used type rather than the sum of applications across all types of genital powder exposure. We reasoned that contemporaneous powder applications were unlikely to be independent events and therefore should not be treated cumulatively. Analyses of estimated lifetime number of applications excluded participants in the HOP study as data on age and frequency of use were not collected ($n = 2,224$); genital powder users' missing information on duration or frequency of use were omitted in the remaining studies ($n = 394$). Never-regular users of genital powders and women who only reported nongenital use were coded as having zero lifetime genital powder applications and comprised the reference group for this analysis. Categories were determined on the basis of age-specific quartile cutoff points in controls (25th, 50th, and 75th percentile cutoff points are 612, 1,872, and 5,400 for participants < 40 years old; 612, 2,160, and 7,200 for 41–50 years; 720, 3,600, and 10,800 for 51–60 years; 1,440, 5,760, and 14,440 for 61–70; 840, 7,200, and 18,000 for > 70 years). Trends were evaluated on the basis of the median lifetime number of genital powder applications for controls in each age-specific quartile using the Wald statistic and were conducted both including and excluding never users of genital powders.

We estimated the association between genital powder use and ovarian cancer risk within strata to evaluate potential modification of effect defined using a cutoff point BMI of 30 based on the World Health Organization's definition of obesity, endometriosis, parity, tubal ligation/hysterectomy, and menopausal status. We used likelihood-ratio statistics comparing models with and without interaction terms to determine statistically significant interactions. To estimate calendar year of first use, we subtracted the years since first use (age at study entry minus age at first genital powder use) from median calendar year of the participant's study.

All analyses were conducted in SAS v9.2 (SAS) and Stata v9.2 (StataCorp). All P values are two-sided. Analyses have been independently verified by two separate study groups (HAW and NCO).

Results

This pooled analysis of eight case–control studies included 9,859 controls and 8,525 ovarian cancer cases. Genital powder use was reported by 2,511 (25%) of the controls and 2,600 (31%) of the cases, whereas powder use only on other (nongenital) parts of the body was reported by 1,533 (16%) of the controls and 1,282 (15%) of the cases (Table 2). The prevalence of genital powder use in controls varied widely between study sites, highest in AUS (45%) and lowest in HAW (15%; Table 3).

In the pooled analysis, ever-regular use of genital powder was associated with a modest increase in risk of ovarian cancer (OR, 1.24; 95% CI, 1.15–1.33; Table 3) relative to women who reported no powder use (AUS, HAW, HOP,

Table 2. Characteristics of cases and controls included in the pooled analysis[a]

	Controls (N = 9,859) Mean (STD) or N (%)	Cases (N = 8,525) Mean (STD) or N (%)
Age	55 (12)	55 (12)
Oral contraceptive use		
Never	2,995 (30)	3,411 (40)
Ever	6,864 (70)	5,114 (60)
Parous		
No	1,468 (15)	2,196 (26)
Yes	8,391 (85)	6,329 (74)
Tubal ligation		
No	7,359 (75)	6,994 (82)
Yes	2,500 (25)	1,531 (18)
BMI	26.5 (6.1)	27.0 (6.6)
Race/ethnicity		
Non-Hispanic White	8,629 (88)	7,433 (87)
Hispanic White	197 (2)	214 (3)
Black	273 (3)	268 (3)
Asian	350 (4)	313 (4)
Other[b]	407 (4)	291 (4)
Powder use[c]		
Never use	5,815 (59)	4,643 (54)
Non-genital use only	1,533 (16)	1,282 (15)
Genital use	2,511 (25)	2,600 (31)

[a]All characteristics listed except age differed significantly (<0.01) between cases and controls. Cases include both borderline and invasive ovarian cancers.
[b]There are 6 cases and 3 controls missing race/ethnicity information.
[c]Categories for non-genital and genital powder use are mutually exclusive.

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Table 3. Association between powder use and risk of ovarian cancer (borderline and invasive combined) by study site

Site	Controls (%) (N = 9,859)	Cases (%) (N = 8,525)	Age-adjusted OR (95% CI)[a]	Multivariate OR (95% CI)[a]
AUS				
No powder use	305 (21)	300 (21)	1.00	1.00
Non-genital use only	486 (34)	427 (30)	0.85 (0.69–1.05)	0.92 (0.74–1.14)
Genital use	658 (45)	705 (49)	1.04 (0.85–1.26)	1.13 (0.92–1.38)
DOV[b]				
No powder use	1,544 (83)	1,293 (83)	1.00	1.00
Genital use	297 (16)	272 (17)	1.14 (0.95–1.37)	1.13 (0.93–1.36)
HAW				
No powder use	489 (65)	326 (68)	1.00	1.00
Non-genital use only	154 (20)	81 (17)	0.79 (0.58–1.07)	0.69 (0.50–0.96)
Genital use	112 (15)	74 (15)	0.99 (0.72–1.37)	0.99 (0.70–1.41)
HOP				
No powder use	989 (66)	439 (60)	1.00	1.00
Non-genital use only	184 (13)	102 (14)	1.23 (0.94–1.61)	1.23 (0.93–1.62)
Genital use	316 (21)	194 (26)	1.37 (1.11–1.69)	1.34 (1.07–1.67)
NCO				
No powder use	391 (60)	469 (60)	1.00	1.00
Non-genital use only	137 (21)	122 (16)	0.75 (0.57–0.99)	0.74 (0.56–0.99)
Genital use	122 (19)	195 (25)	1.33 (1.03–1.74)	1.37 (1.05–1.80)
NEC				
No powder use	1,239 (53)	1,129 (49)	1.00	1.00
Non-genital use only	454 (19)	421 (18)	1.02 (0.87–1.19)	1.04 (0.88–1.22)
Genital use	636 (27)	755 (33)	1.30 (1.14–1.49)	1.28 (1.12–1.47)
SON[b]				
No powder use	364 (65)	252 (56)	1.00	1.00
Genital use	200 (35)	197 (44)	1.43 (1.11–1.85)	1.35 (1.03–1.76)
USC				
No powder use	494 (63)	435 (56)	1.00	1.00
Non-genital use only	118 (15)	129 (17)	1.25 (0.94–1.66)	1.14 (0.85–1.52)
Genital use	170 (22)	208 (27)	1.39 (1.10–1.77)	1.36 (1.06–1.74)
Pooled[c]				
No powder use	5,815 (59)	4,643 (54)	1.00	1.00
Non-genital use only	1,533 (16)	1,282 (15)	0.98 (0.90–1.07)	0.98 (0.89–1.07)
Genital use	2,511 (25)	2,600 (31)	1.25 (1.16–1.34)	1.24 (1.15–1.33)

[a]Study-specific estimates were determined using unconditional logistic regression and pooled ORs were estimated using conditional logistic regression conditioned on 5-year age groups and study. Multivariate models are adjusted for age (continuous), oral contraceptive duration (never use, <2, 2–<5, 5–<10, or ≥10 years), parity (0, 1, 2, 3, or 4+ children), tubal ligation history (no or yes), BMI (quartiles), race/ethnicity (non-Hispanic White, Hispanic White, Black, Asian, or other).
[b]Information on non-genital powder use was not collected in the SON and DOV study.
[c]*P* value for heterogeneity between multivariate study specific ORs equal to 0.61; calculated using Conchran's Q statistic test.

NCO, NEC, and USC) or no genital powder use (DOV and SON). We observed no heterogeneity in the risk associated with genital powder use between studies regardless of the reference group ($P = 0.61$; Fig. 1). Results were similar for genital powder users compared with a combined reference group including never users and women whose use of powder was exclusively non-genital (covariate-adjusted OR, 1.25; 95% CI, 1.16–1.34; data not shown), reflecting the absence of an association between powder use on other parts of the body with ovarian cancer risk (Table 3).

Genital powder use was associated with a similar increased risk of borderline and invasive ovarian cancer overall (Table 4). For borderline tumors, the association was stronger for the serous subtype (OR, 1.46; 95% CI, 1.24–1.72; Table 4) and nonsignificant for the mucinous subtype. For invasive ovarian cancer, we observed small

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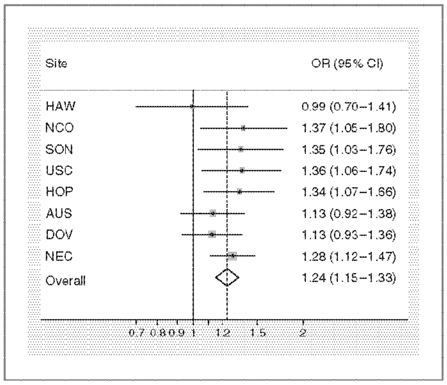

Figure 1. Association between genital powder use and ovarian cancer risk in eight studies, $P_{heterogeneity} = 0.61$. Adjusted for age (continuous), oral contraceptive duration (never use, <2, 2–<5, 5–<10, or ≥10 years), parity (0, 1, 2, 3, or 4+ children), tubal ligation history, BMI (quartiles), race/ethnicity (non-Hispanic White, Hispanic White, Black, Asian, or other) and non-genital powder use. Studies listed in decreasing order of effect size SE (funnel plot). No evidence of heterogeneity based on Conchran's Q statistic ($P = 0.61$).

increases in risk of serous (OR, 1.20; 95% CI, 1.09–1.32), endometrioid (OR, 1.22; 95% CI, 1.04–1.43), and clear cell (OR, 1.24; 95% CI, 1.01–1.52) cancer but no significant increase in risk of mucinous cancer (OR, 1.09; 95% CI, 0.84–1.42). Similarly, we observed no significant increase in risk when borderline and invasive mucinous tumors were considered together (data not shown). Risk associated with genital powder use was consistent across studies for borderline and invasive tumors as well as invasive serous, endometrioid, and clear cell subtypes ($P_{heterogeneity} > 0.1$; Fig. 2A–E), but not for mucinous tumors ($P = 0.08$; Fig. 2F). Genital powder use was associated with increased risk of invasive mucinous tumors in SON, HOP (significantly), and USC (nonsignificantly), whereas in the remaining studies (HAW, NCO, AUS, DOV, and NEC) genital powder use was nonsignificantly associated with reduced risk.

We evaluated cumulative genital powder exposure as a composite variable of frequency and duration of use. We observed similar increased risks of all nonmucinous subtypes of epithelial ovarian cancer combined across quartiles of genital powder compared with nonuse: OR_{Q1}, 1.18; 95% CI, 1.02–1.36; OR_{Q2}, 1.22; 95% CI, 1.06–1.41; OR_{Q3}, 1.22; 95% CI, 1.06–1.40; OR_{Q4}, 1.37; 95% CI, 1.19–1.58 (Table 5). Although a significant increase in risk with an increasing number of genital powder applications was found for nonmucinous epithelial ovarian cancer when nonusers were included in the analysis ($P_{trend} < 0.0001$), no trend in cumulative use was evident in analyses restricted to ever-users of genital powder ($P_{trend} = 0.17$; Table 5). Taken together, these observations suggest that the significant trend test largely reflects the comparison of ever-regular use with never use. Because tubal ligation or hysterectomy would block the transport of powder through the genital tract to the ovaries, we conducted a sensitivity analysis excluding women who started genital powder use after these procedures. We observed similar associations when

Table 4. Association between powder use and risk of ovarian cancer by behavior and histology

	Model 1[a]			Model 2[a]		
	No powder use n (%)	Genital powder use n (%)	OR (95% CI)[b]	No genital powder use n (%)	Genital powder use n (%)	OR (95% CI)[b]
Controls	5,815 (59)	2,511 (25)		7,348 (75)	2,511 (25)	
All borderline cases	1,035 (58)	504 (28)	1.29 (1.14–1.48)	1,247 (72)	504 (28)	1.30 (1.15–1.47)
Serous	567 (57)	300 (30)	1.46 (1.24–1.72)	700 (70)	300 (30)	1.45 (1.24–1.69)
Mucinous	409 (60)	184 (27)	1.17 (0.96–1.42)	502 (73)	184 (27)	1.19 (0.98–1.43)
All invasive cases	3,470 (54)	2,009 (31)	1.21 (1.12–1.32)	4,471 (69)	2,009 (31)	1.23 (1.14–1.32)
Serous	1,952 (53)	1,197 (32)	1.20 (1.09–1.32)	2,519 (68)	1,197 (32)	1.24 (1.13–1.35)
Mucinous	206 (57)	94 (26)	1.09 (0.84–1.42)	269 (74)	94 (26)	1.06 (0.82–1.36)
Endometrioid	568 (55)	304 (30)	1.22 (1.04–1.43)	723 (70)	304 (30)	1.20 (1.03–1.40)
Clear Cell	327 (54)	187 (31)	1.24 (1.01–1.52)	420 (69)	187 (31)	1.26 (1.04–1.52)

[a]In model 1, the reference group is restricted to women with no powder use except for the DOV and SON studies as these did not collect data on non-genital powder use. The number of cases who reported non-genital powder use was 212 (13%) of all borderline cases, 133 (13%) serous borderline, 93 (14%) mucinous borderline, 1,001 (15%) of all invasive, 567 (15%) serous invasive, 63 (17%) mucinous invasive, 155 (15%) endometrioid invasive, 93 (15%) clear cell invasive. In model 2, the reference group includes all women who did not use genital powders (nonusers and non-genital users combined).
[b]ORs were estimated using conditional logistic regression conditioned on 5-year age groups and adjusted for age (continuous), oral contraceptive duration (never use, <2, 2–<5, 5–<10, or ≥10 years), parity (0, 1, 2, 3, or 4+ children), tubal ligation history (no or yes), BMI (quartiles), race/ethnicity (non-Hispanic White, Hispanic White, Black, Asian, or other).

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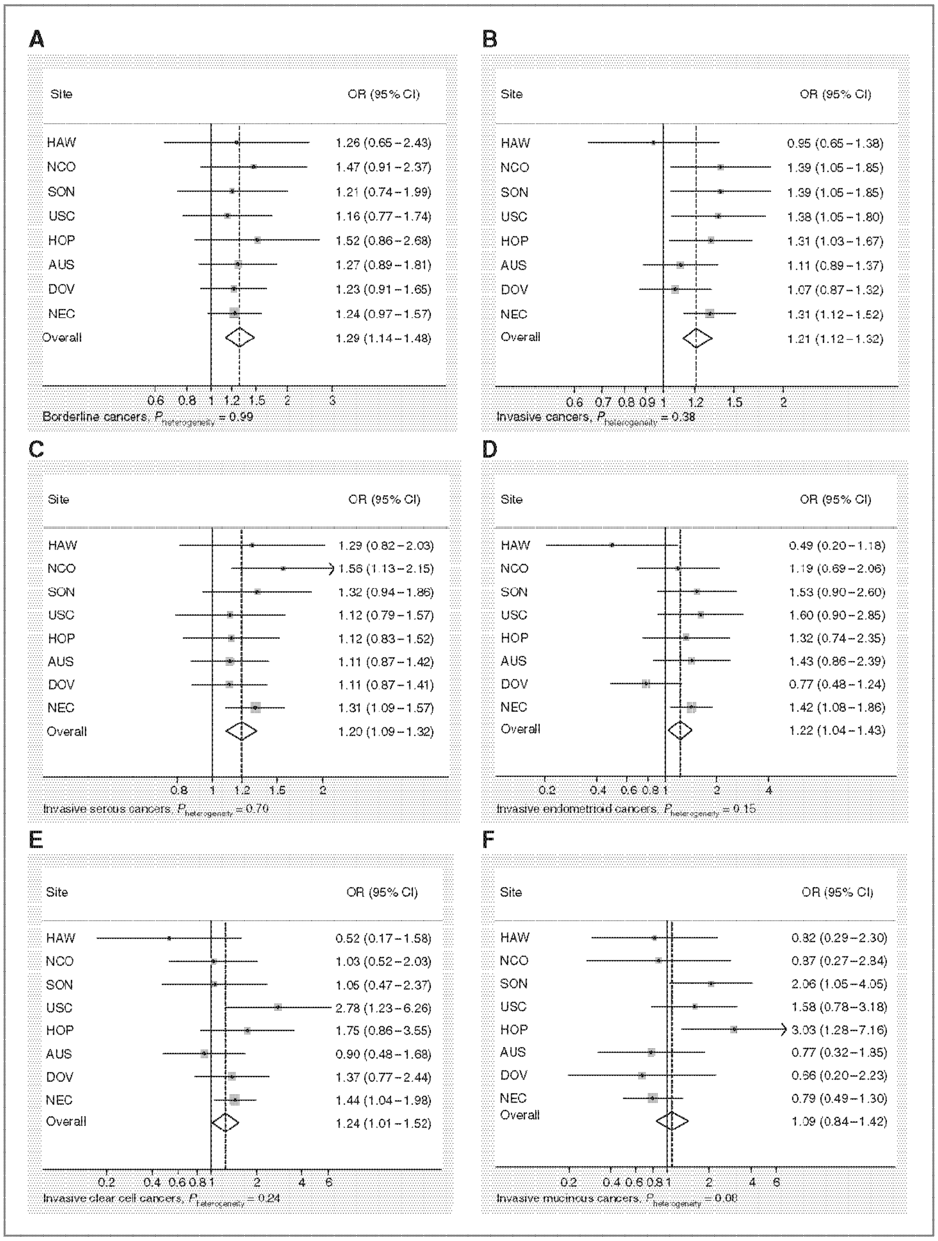

Figure 2. Association between genital powder use and subgroups of ovarian cancer defined by behavior and histology (A, Borderline, B, Invasive, C, Invasive serous, D, Invasive endometrioid, E, Invasive clear cell, F, mucinous.). Estimates are adjusted for the same covariates as in the model presented in Fig. 1.

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Table 5. Association between estimated lifetime applications of genital powder and risk of ovarian cancer (borderline and invasive combined)

Lifetime number of applications[a]		All cases (N = 7,587)		Nonmucinous cases (N = 6,361)	
	Controls (%)	Cases (%)	OR[b] (95% CI)	Cases (%)	OR[b] (95% CI)
Never users	6,175 (76)	5,384 (71)	1.00	4,472 (70)	1.00
Quartile 1	509 (6)	534 (7)	1.14 (1.00–1.31)	467 (7)	1.18 (1.02–1.36)
Quartile 2	512 (6)	541 (7)	1.23 (1.08–1.41)	456 (7)	1.22 (1.06–1.41)
Quartile 3	497 (6)	542 (7)	1.22 (1.07–1.40)	457 (7)	1.22 (1.06–1.40)
Quartile 4	486 (6)	586 (8)	1.32 (1.16–1.52)	509 (8)	1.37 (1.19–1.58)
P_{trend}[c]			0.17		0.17

[a]Age-specific 25th, 50th, and 75th percentile cutoff points are 612, 1,872, and 5,400 for participants < 40 years old; 612, 2,160, and 7,200 for 41–50 years; 720, 3,600, and 10,800 for 51–60 years; 1,440, 5,760, and 14,440 for 61–70; 840, 7,200, and 18,000 for > 70 years.
[b]ORs were estimated using conditional logistic regression conditioned on 5-year age groups and adjusted for age (continuous), oral contraceptive duration (never use, <2, 2–<5, 5–<10, or ≥10 years), parity (0, 1, 2, 3, or 4+ children), tubal ligation history (no or yes), BMI (quartiles), race/ethnicity (non-Hispanic White, Hispanic White, Black, Asian, or other).
[c]Trend excludes never users.

we excluded the 65 cases and 79 controls who started genital powder use for the first time after surgery (OR_{Q1}, 1.19; 95% CI, 1.03–1.38; OR_{Q2}, 1.19; 95% CI, 1.03–1.38; OR_{Q3}, 1.21; 95% CI, 1.04–1.39; OR_{Q4}, 1.36; 95% CI, 1.18–1.57). For studies that collected data on timing of powder use and tubal ligation/hysterectomy, we were able to identify timing of genital powder exposure in relation to surgery based on age of powder use and age at surgery. Restricting our exposure to genital powder applications that occurred before tubal ligation or hysterectomy made no substantive difference in the results.

The association between any genital powder use and ovarian cancer risk was stronger among women with BMI < 30 kg/m^2 (OR, 1.28; 95% CI, 1.17–1.39) than for women with BMI ≥ 30 (OR, 1.14; 95% CI, 0.98–1.32; $P_{interaction}$ = 0.01). We observed no significant interactions between genital powder use and parity, reported history of endometriosis, tubal ligation/hysterectomy, or menopausal status (all $P_{interaction} > 0.1$). The association between genital powder use and ovarian cancer risk was similar for women who started use between 1952 and 1961 (OR, 1.36; 95% CI, 1.19–1.56), between 1962 and 1972 (OR, 1.27; 95% CI, 1.11–1.46), and after 1972 (OR, 1.31; 95% CI, 1.15–1.51). However, we observed an attenuated association for women who started genital powder use before 1952 (OR, 1.08; 95% CI, 0.93–1.25).

Discussion

This pooled analysis of eight case–control studies suggests that genital powder use is associated with a modest 20% to 30% increase in risk of developing epithelial ovarian cancer, including serous, endometrioid, and clear cell tumors, but is less relevant to invasive mucinous tumors. Our findings are consistent with and extend the findings of three meta-analyses that have reported an increased risk of epithelial ovarian cancer with genital powder use (1, 4, 5) by including dose-response and histology-specific analyses. Our estimate of the overall association between genital powder use and ovarian cancer risk was slightly attenuated compared with previous estimates from meta-analyses. Possible reasons for the difference include the lack of restriction to published results, data harmonization between studies that allowed similar definitions for the exposure and covariates, and chance. On the basis of the consistency in the epidemiologic literature on talc-based powder and ovarian cancer risk, the International Agency for Research on Cancer (IARC) classified talc-based body powder as a class 2b carcinogen "possibly carcinogenic to human beings" (29).

The biologic plausibility for the observed association between genital powder use and ovarian cancer risk has been challenged because evidence for dose-response has been inconsistent (2, 4, 5, 9, 10, 15, 22). The lack of significant dose-response may reflect the difficulty inherent in accurate recollection of specific details of frequency and duration of genital powder use. Also, because not all powder products contain talc, various products may differ in their potential carcinogenic effects. Alternatively, the association between genital powder exposure and ovarian cancer risk may not be linear and a modest exposure may be sufficient to increase cancer risk. Talc-containing powders are hypothesized to promote cancer development by ascending the female genital tract and interacting directly with the ovarian surface epithelium, leading to local inflammation characterized by increased rates of cell division, DNA repair, oxidative stress, and elevated inflammatory cytokines (13). Particles in solution easily ascend the genital tract (30, 31). Our finding of slightly attenuated associations following exclusion of women with powder exposure after tubal ligation or hysterectomy are not supportive of this hypothesis, but risk estimates in this subgroup analysis may have randomly differed from those including all women because of the reduction in

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sample size. Talc particles have been observed in the ovaries of humans (32) and in rodent models (33, 34), but little is known about the biologic effects of genital powder use.

In the current analyses of the various histologic subtypes of ovarian cancer, we confirmed previous reports of increased risk of serous invasive tumors with genital powder use (2, 4, 8, 9, 22). We also observed significantly increased risk of both endometrioid and clear cell invasive ovarian tumors with use of genital powder, and this finding was consistent across studies. It has been suggested that both endometrioid and clear cell ovarian tumors may originate from ectopic uterine endometrium (endometriosis) implanted on the ovary (17). In contrast, we observed no significant associations between genital powder use and either borderline or invasive mucinous ovarian cancer. The lack of a significant association for mucinous tumors may be due to the relatively small number of these tumors or could be an indication that powder exposure is not relevant to the pathogenesis of this histologic type. Studies have noted that ovarian cancer risk factors and molecular characteristics differ for mucinous tumors (16–18, 23, 35–39).

Limitations of our pooled analysis include differences in the wording of questions about genital powder use between studies and the retrospective nature of the exposure ascertainment. Women who were classified as genital powder users varied from "ever" use (AUS) or "ever regular" use (SON) to powder use for at least 6 months (HAW, HOP, NCO, NEC, and USC) or at least 1 year (DOV). Differences in genital powder questions result in varying levels of misclassification of true genital powder exposure. However, because exposure definitions are the same for cases and controls within each study, misclassification of genital powder exposure due to the question wording would be nondifferential, leading to an underestimation of the true association for any given study. These studies were retrospective in nature and therefore potentially susceptible to bias if cases were more likely to report genital powder use than controls. Although nongenital powder use was not associated with ovarian cancer risk, it is nevertheless possible that any over-reporting of powder use by cases might have been limited to reporting of genital powder. Our analyses were also limited by missing data on genital powder use; however, missingness was not associated with the distribution of any of the ovarian cancer risk factors examined and was thus not likely to bias our results. Strengths of our analysis include a large sample size and pooled analysis of individual data, allowing evaluation of the association of genital powder use with less common histologic subgroups of ovarian cancer, careful harmonization of the data based on comparison of study questionnaires, the use of a composite variable combining duration, and frequency to assess dose–response relationships.

In conclusion, our large pooled analysis of case–control studies shows a small-to-moderate (20%–30%) increased risk of ovarian cancer with genital powder use, most clearly pertaining to nonmucinous epithelial ovarian tumors. More work is needed to understand how genital powders may exert a carcinogenic effect, and which constituents (e.g., talc) may be involved. Because there are few modifiable risk factors for ovarian cancer, avoidance of genital powders may be a possible strategy to reduce ovarian cancer incidence.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): K.L. Terry, S. Karageorgi, Y.B. Shvetsov, M.A. Merritt, R.P. Weber, L. Akushevich, W.-H. Lo-Ciganic, W. Sieh, J.A. Doherty, A. Berchuck, C.L. Pearce, R.B. Ness, P.M. Webb, M.A. Rossing, H. Risch, M.T. Goodman
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Study supervision: H. Risch

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Cancer Prevention Research

Genital Powder Use and Risk of Ovarian Cancer: A Pooled Analysis of 8,525 Cases and 9,859 Controls

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GENITAL TALC EXPOSURE AND RISK OF OVARIAN CANCER

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Epidemiologic studies have suggested an increased risk for ovarian cancer associated with the use of talcum powder in genital hygiene, but the biologic credibility of the association has been questioned. We conducted a population-based case-control study in eastern Massachusetts and New Hampshire involving 563 women with newly diagnosed epithelial ovarian cancer and 523 control women selected either by random digit dialing or through lists of residents. Use of body powders was assessed through personal interview and the exposure odds ratio (OR) for the use of talc in genital hygiene was calculated. Cases were more likely than controls (45% *vs.* 36%) to have used talc as a body powder in some manner, and the excess was confined to patients who used talc on the perineum directly or as a dusting powder to underwear or sanitary napkins. Relative to women who never used body powder or used it only in non-genital areas, the OR (and 95% confidence interval) associated with genital exposure to talc was 1.60 (1.18 and 2.15) after adjustment for age, study location, parity, oral contraceptive use, body mass index and family history of breast or ovarian cancer. Exposure prior to rather than after a first livebirth appeared to be more harmful, and the association was most apparent for women with invasive serous cancers and least apparent for those with mucinous tumors. We conclude that there is a significant association between the use of talc in genital hygiene and risk of epithelial ovarian cancer that, when viewed in perspective of published data on this association, warrants more formal public health warnings. *Int. J. Cancer* 81:351–356, 1999.
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An association between the use of talc in genital hygiene and ovarian cancer was first examined in an epidemiologic study in 1982 (Cramer *et al.*, 1982). An elevated odds ratio for genital talc exposure was observed in this study, in 8 of the largest subsequent epidemiological studies (Whittemore *et al.*, 1988; Booth *et al.*, 1989; Harlow *et al.*, 1992; Chen *et al.*, 1992; Purdie *et al.*, 1995; Shushan *et al.*, 1996; Cook *et al.*, 1997; Chang and Risch, 1997) and in a study of borderline tumors (Harlow and Weiss, 1989). Only 3 smaller studies reported a null association (Hartge *et al.*, 1983; Rosenblatt *et al.*, 1992, Tzonou *et al.*, 1993). Despite this consistency, the association is still viewed with skepticism based upon weak odds ratios, poor dose-response relationships and an incomplete understanding of the biological mechanism by which talc might lead to ovarian cancer. We have completed a large population-based case-control study of ovarian cancer which offers new perspectives on the validity of the talc and ovarian cancer association.

MATERIAL AND METHODS

We conducted a population-based case-control study of women with newly diagnosed ovarian cancer who resided in eastern Massachusetts (MA) or New Hampshire (NH). Women with ovarian cancer were identified through hospital tumor boards and statewide cancer registries. Between 5/92 and 3/97, 1,080 cases of ovarian cancer were identified. After excluding 203 cases who had died or moved, had no telephone, did not speak English or had a non-ovarian primary tumor after review, 877 women remained eligible. Physicians denied permission to contact 126 (14%) of these women, and 136 cases (16%) declined to participate. Our analysis is based upon data from 563 cases with epithelial ovarian cancer, including those with tumors of borderline malignancy.

We identified control women using random digit dialing (RDD) in which the sampling unit for an interviewed case comprised the 99 telephone numbers generated from the first 5 digits of her telephone number plus all remaining combinations of the last 2 digits (excluding the case's own number). These numbers were listed in random order and called to screen households for potential controls who were within 4 years of the age of the case. Excluding business and non-working numbers, approximately 5,400 calls yielded 10% of households in which the household member declined to provide a household census and 80% of households in which an age and sex matched control for a case could not be made or a potential control was ineligible because of a prior oophorectomy. Of the remaining 10% of households screened with a potential eligible control, 72% agreed to participate. RDD proved inefficient for identifying controls over age 60 in MA since a substantially greater number of households needed to be screened to obtain an older control. Except in NH where complete listings of residents were unavailable, we chose to identify older controls in MA by randomly selecting women through use of lists (townbooks) of all residents in towns by name, age, and address according to precinct. We matched older controls to cases by community and age within 4 years based on the townbooks. Of 328 sampled townbook controls, 21% could not be reached, 18% were ineligible and 30% declined to participate. This analysis includes a total of 523 RDD and townbook controls.

In introducing the study to potential cases and controls, specific hypotheses including the talc association were not discussed. After written informed consent, we assessed demographic information, menstrual and reproductive history, medical and family history and personal habits using an in-person interview. We assessed exposures occurring prior to a "reference date," defined as 1 year before the date of diagnosis for cases and the date of interview for controls. We asked whether women had "regularly used talc, baby, or deodorizing powders dusted or sprayed" to feet, arms or other non-genital areas, to the genital or rectal area, on sanitary napkins, or on underwear, with the latter 3 methods defined as "genital exposure" and either no use or use in non-genital areas defined as "no genital exposure." A husband's use of powder in his genital area was also assessed. Age at first use, types of powder(s) used, applications per month and total years of use in genital hygiene were assessed in talc users. We did not assess potential talc exposure from diaphragms or condoms, exposures not found to be associated with ovarian cancer in our previous studies (Cramer *et al.*, 1982; Harlow *et al.*, 1992).

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TABLE I – PERINEAL TALC EXPOSURE[1] IN RELATION TO OVARIAN CANCER RISK BY CHARACTERISTICS OF STUDY PARTICIPANTS

	Cases		Controls			
	Total	Talc exposure (%)	Total	Talc exposure (%)	Age-adjusted[2] OR	(95% C.I.)
Age						
<50	266	66 (24.8)	262	43 (16.4)	1.68	(1.09, 2.58)
≥50	297	86 (29.0)	261	52 (19.9)	1.64	(1.11, 2.43)
Study center						
MA	433	126 (29.1)	411	85 (20.7)	1.56	(1.14, 2.14)
NH	130	26 (20.0)	112	10 (8.9)	2.49	(1.14, 5.45)
Education						
≤12	218	58 (26.6)	171	28 (16.4)	1.79	(1.08, 2.97)
>12	344	93 (27.0)	352	67 (19.0)	1.59	(1.10, 2.27)
Marital status						
Never married	110	31 (28.2)	61	10 (16.4)	1.77	(0.78, 4.00)
Ever married	453	121 (26.7)	462	85 (18.4)	1.62	(1.18, 2.22)
Religion						
Jewish	54	18 (33.3)	44	10 (22.7)	1.69	(0.68, 4.18)
Non-Jewish	509	134 (26.3)	479	85 (17.8)	1.63	(1.20, 2.22)
Weight						
<140	237	57 (24.0)	247	40 (16.2)	1.60	(1.02, 2.53)
≥140	326	95 (29.1)	275	55 (20.0)	1.65	(1.13, 2.42)
Use of OCs (months)						
<3 or never	334	98 (29.3)	247	52 (21.0)	1.55	(1.06, 2.28)
≥3	229	54 (23.6)	276	43 (15.6)	1.67	(1.07, 2.61)
Number of liveborn children						
0	185	55 (29.7)	106	20 (18.9)	1.65	(0.92, 2.98)
1–2	212	49 (23.1)	209	34 (16.3)	1.56	(0.95, 2.54)
3+	166	48 (28.9)	208	41 (19.7)	1.69	(1.04, 2.75)
Prior tubal ligation						
No	488	135 (27.7)	437	76 (17.4)	1.80	(1.31, 2.47)
Yes	75	17 (22.7)	86	19 (22.1)	0.98	(0.46, 2.08)
Prior hysterectomy						
No	529	139 (26.3)	487	88 (18.1)	1.60	(1.18, 2.16)
Yes[3]	34	13 (38.2)	36	7 (19.4)	2.61	(0.88, 7.78)
Family history of breast or ovarian cancer						
No	481	132 (27.4)	462	87 (18.8)	1.59	(1.17, 2.17)
Yes	82	20 (24.4)	61	8 (13.1)	2.21	(0.89, 5.48)

OR: odds ratio; CI: confidence interval; OCs: oral contraceptives.–[1]Sources of perineal talc exposure include dusting of underwear, diaphragms, sanitary napkins and/or dusting of genital area.–[2]Adjusted for age as a continuous variable.–[3]Excludes those with tubal ligation prior to hysterectomy.

For all cases studied, we reviewed pathology reports and sought slides in any instance where there was a discrepancy between histologic description and final diagnosis. After completing the review, cases were grouped according to the following histologic categories: serous cancers (including serous cystadenocarcinomas and surface papillary carcinomas), mucinous cancers, endometrioid and clear cell cancers, including mixed mesodermal or mixed epithelial with an endometrioid or clear cell component) and undifferentiated or other cancers. According to Young *et al.* (1994), serous tumors tend to be either borderline or invasive and seldom display a mixture while borderline and invasive grades often intermingle within other histologic types, especially the mucinous tumors. Based on this tendency, only serous borderline tumors were distinguished from invasive cancers when considering odds ratios by histologic type and grade.

Since matching was performed as the most convenient means for selecting controls comparable to cases in age and geographic locale and not as the principal means of controlling for confounding, matching was not preserved in the analysis. We analyzed our data by constructing frequency counts of cases and controls by study variables and by calculating crude odds ratios (OR). We then used unconditional logistic regression to adjust for the matching variables including age (continuous), study site (MA, NH), body mass index (continuous), which might have influenced likelihood of using body powder, and for variables strongly linked to ovarian cancer risk such as parity (0, 1), oral contraceptive use (never or <3 months, ≥3 months) and family history of breast or ovarian cancer (no, yes) and tubal ligation (no, yes). Most analyses were performed by using the SAS system (SAS Institute, Cary, NC). Tests for linear trend were performed using the likelihood ratio test with continuous forms of the talc variables. Frequency counts from studies included in our review of published studies were entered into STATA (College Station, TX) to compute crude and combined odds ratios.

RESULTS

Table I summarizes data regarding how cases and controls differed demographically and by known risk factors for ovarian cancer, how these same variables influenced genital talc exposure among controls and how the association between talc use in the genital area and ovarian cancer varied among strata. Controls were more likely than cases to have gone beyond high school, to have married, to have had children and to have used oral contraceptives. In examining the frequency of talc use among controls, only study location significantly influenced likelihood of genital talc exposure. Women from New Hampshire were less likely to have used talc in the genital area compared to women from Massachusetts. Ovarian cancer cases in almost all strata were more likely to have used powder genitally compared to controls, with corresponding elevated odds ratios. A notable exception was the lack of an association between talc use and ovarian cancer among women who reported having had a tubal ligation.

Table II shows adjusted odds ratios by manner, type and frequency of powder use. A greater percentage of cases had regularly used powder in some manner compared to the controls.

TABLE II – ADJUSTED ODDS RATIOS FOR OVARIAN CANCER ASSOCIATED WITH TYPES AND FREQUENCY OF POWDER USE

Type of personal use	Cases Number (%)	Controls Number (%)	Adjusted OR[1]	(95% C.I.)
No personal use	312 (55.4)	334 (63.9)	1.0	
Use, non-genital areas	99 (17.6)	94 (18.0)	1.08	(0.77, 1.50)
Use, dusting perineum	71 (12.6)	51 (9.8)	1.45	(0.97, 2.18)
Use, dusting sanitary napkin	20 (3.6)	12 (2.3)	1.45	(0.68, 3.09)
Use, dusting underwear	8 (1.4)	6 (1.2)	1.21	(0.40, 3.64)
Multiple uses genital area	53 (9.4)	26 (5.0)	2.15	(1.30, 3.57)
Genital use				
No personal genital exposure	411 (73.0)	428 (81.8)	1.0	
Any personal genital exposure	152 (27.0)	95 (18.2)	1.60	(1.18, 2.15)
Longest used type of powder[2]				
No genital use	411 (73.4)	428 (81.8)	1.0	
Talc	148 (26.4)	92 (17.6)	1.69	(1.26, 2.27)
Cornstarch	1 (0.2)	3 (0.6)	0.31	(0.03, 3.01)
Husband use[3,1]				
No	291 (87.6)	346 (92.0)	1.0	
Yes	41 (12.4)	30 (8.00)	1.52	(0.92, 2.52)
Frequency of use per month[4]				
<30	64 (11.5)	28 (5.4)	2.21	(1.37, 3.56)
30–39	59 (10.6)	51 (9.8)	1.17	(0.78, 1.76)
40+	23 (9.8)	15 (2.9)	1.57	(0.80, 3.10)

[1]Adjusted for age (continuous), study center (MA, NH), tubal ligation (ever, never), BMI (continuous), parity (0, ≥1), OC use (<3 months, ≥3 months), and primary relative with breast or ovarian cancer (yes, no) and other categories of genital talc use, except where noted.–[2]Adjusted for age (continuous), study center (MA, NH), and tubal ligation (ever, never) and other powder.–[3]Among married women with no personal genital talc use.–[4]Total of all uses in the genital area.

Relative to those with no use of a body powder, those who used powder only in non-genital areas did not have an increased risk of ovarian cancer [OR=1.08 (0.77 and 1.50)]. However, elevated ORs and (95% CI) were observed for women who directly powdered the genital or rectal area [1.45 (0.97 and 2.18)]; who dusted sanitary napkins: 1.45 (0.68 and 3.09); who dusted underwear [1.21 (0.40 and 3.64)] and who used powder in multiple ways in the genital area [2.15 (1.30 and 3.57)]. There was a significant excess of cases who regularly used powder in some manner in the genital area, and the adjusted OR was similar whether the non exposed referent group was considered to be women with no use of talc anywhere [OR= 1.58, (1.16 and 2.16)] or women with no genital use including those who used it as a body powder in non-genital areas [OR= 1.60 (1.18 and 2.15)]. Few of the women in our study reported use of cornstarch rather than a talc-based powder leading to an imprecise and non-significant OR for ovarian cancer risk associated with its use in the genital area. Among married women who never personally used talc in the genital area, there was an increase of borderline significance in ovarian cancer risk for women whose husbands had used talc in their genital area [OR=1.52 (0.92, 2.52)]. When we examined all methods of genital talc use (except exposure from a husband), we found that most of those who used talc had 30 or more applications per month, but there was no apparent trend for increasing risk for ovarian cancer with increasing number of monthly applications.

Table III examines risk for ovarian cancer associated with ordinal categories related to duration or intensity of talc exposure in the genital area relative to women who never used talc or who used it only in non-genital areas. No clear linear trend was apparent in ORs for categories of age at first use, years of use or total applications. To examine dose response, each of these variables was used as a continuous variable in multivariate models. Linear trends were significant only in those models that included women who were not exposed. To duplicate an analysis performed in a previous report (Harlow *et al.*, 1992), we examined total applications censored by excluding use after closure of the female tract or during non-ovulatory years. Although the ORs for the categories displayed a trend, once again only the multivariate model including the non-genitally exposed revealed a significant trend.

Table IV presents a more detailed analysis of the effect of genital use of talc in women who had no pregnancies at all, in women who had a pregnancy not resulting in a liveborn and in women with a liveborn pregnancy. In the latter 2 groups, we examined risk for ovarian cancer with the timing of talc use in relation to the first pregnancy. Genital talc use that began after a first pregnancy appeared to be associated with lower risk compared to use which began before the first pregnancy. The effect was more apparent among those with a liveborn. Eighty-five of 374 parous cases used at least some talc prior to their first liveborn compared to 64 of 416 parous controls, leading to an adjusted OR (95% CI) of 1.58 (1.10 and 2.29). In contrast, 8 of 378 parous cases used talc only after their first livebirth compared to 10 of 417 parous controls, leading to an adjusted OR(95% CI) of 0.97 (0.38 and 2.50) for ovarian cancer associated with talc use after a first livebirth.

Table V shows the average age and use of genital talc for all controls and for cases by histologic type of ovarian cancer. Average age differed by histologic type but did not account for the differences in ORs. The odd ratio for genital talc use was greatest (and significant) for invasive serous tumors and less than 1 only for mucinous tumors (invasive and borderline combined) after adjustment for age and other covariates.

DISCUSSION

Consistent with four recent case-control studies of ovarian cancer (Purdie *et al.*, 1995, Sushan *et al.*, 1996, Cook *et al.*, 1997, Chang and Risch, 1997), our results demonstrate a significant association between the use of talc in genital hygiene and risk for ovarian cancer. In our discussion, we will examine whether this association satisfies traditional criteria for a causal association including consistency and strength of the association, potential biases, dose response and biological credibility.

Figure 1 summarizes data on risk for ovarian cancer with any genital use of talc from 14 case-control studies including this one. The combined odds ratio and 95% CI is 1.36 (1.24 and 1.49), which is statistically significant. Odds ratios deviating most from the pooled value were observed in the smaller studies, and the test for heterogeneity was not significant (p=0.085). Thus, the criteria for

TABLE III – ADJUSTED ODDS RATIOS FOR OVARIAN CANCER ASSOCIATED WITH GENITAL USE OF TALC

Type of exposure	Cases Number (%)	Controls Number (%)	Adjusted OR[1]	(95% C.I.)
No genital use	411 (73.0)	428 (81.8)	1.0	
Age at first use				
<20	97 (17.4)	67 (12.8)	1.46	(1.03, 2.07)
20–25	36 (6.5)	18 (3.4)	1.87	(1.03, 3.39)
>25	13 (2.3)	9 (1.7)	1.54	(0.64, 3.72)
p-value for linear trend is 0.504 excluding non-exposed.				
Years of use				
<20	55 (9.9)	31 (5.9)	1.86	(1.16, 3.00)
20–30	32 (5.8)	26 (5.0)	1.33	(0.76, 2.30)
>30	59 (10.6)	37 (7.1)	1.44	(0.91, 2.26)
p-value for linear trend is 0.477 excluding non-genitally exposed and 0.062 including non-genitally exposed.				
Total applications				
<3000	51 (9.2)	27 (5.2)	1.84	(1.12, 3.03)
3000–10,000	36 (6.5)	28 (5.4)	1.43	(0.84, 2.41)
>10,000	59 (10.6)	39 (7.5)	1.43	(0.92, 2.22)
p-value for linear trend is 0.164 excluding non-genitally exposed and 0.472 including non-genitally exposed.				
Applications censored[2]				
<3000	59 (10.6)	41 (7.8)	1.54	(1.01, 2.35)
3000–10,000	51 (9.2)	31 (5.9)	1.72	(1.08, 2.76)
>10,000	36 (6.5)	20 (3.8)	1.80	(1.02, 3.18)
p-value for linear trend is 0.675 excluding non-genitally exposed and 0.022 including non-genitally exposed.				

[1]Adjusted for age (continuous), study center (MA, NH), BMI (continuous), primary relative with breast or ovarian cancer (yes, no), parity (0, ≥1), OC use (<3 months, ≥3 months), tubal ligation, and other categories of genital talc use, except where noted.–[2]Excludes applications following hysterectomy or tubal ligation and applications during pregnancy and periods of OC use. Adjusted for age (continuous), study center (MA, NH), BMI (continuous) and primary relative with breast or ovarian cancer (yes, no).

TABLE IV – EVER USE OF TALC IN THE GENITAL AREA IN RELATION TO PREGNANCY AND CHILDBIRTH

Group	Cases Total	Cases Number exposed	(%) exposed	Controls Total	Controls Number exposed	(%) exposed	Adjusted OR	95% C.I.
Nulligravid[1]	145	42	(29.0)	82	17	(20.7)	1.48	(0.76, 2.86)
Nulliparous[1] prior to first pregnancy	40	13	(32.5)	24	3	(12.5)	2.80	(0.64, 12.20)
Nulliparous[1] only after first pregnancy	40	2	(5.0)	24	1	(4.2)	1.24	(0.10, 15.32)
Parous[1] prior to first livebirth	374	85	(22.7)	416	64	(15.4)	1.58	(1.10, 2.29)
Parous[2] only after first livebirth	378	8	(2.12)	417	10	(2.40)	0.97	(0.38, 2.50)

[1]Adjusted for age (continuous), study center (MA, NH), BMI (continuous) and primary relative with breast or ovarian cancer (yes, no).–[2]Adjusted for age (continuous), study center (MA, NH), BMI (continuous), primary relative with breast or ovarian cancer (yes, no) and tubal ligation.

TABLE V – HISTORY OF GENITAL TALC USE AND ASSOCIATED ODDS RATIOS BY HISTOLOGIC TYPE AND GRADE

Histologic type/grade	Total	Average age	Any use of genital talc	No use of genital talc	Adjusted OR[1]	(95% CI)
Controls	523	49.3	95	428	1.0	
Histologic type/grade						
Serous borderline	86	41.8	23	63	1.38	(0.82, 2.31)
Serous invasive	229	54.5	72	157	1.70	(1.22, 2.39)
Mucinous	83	46.7	16	67	0.79	(0.44, 1.40)
Endometrioid/clear cell	130	53.9	31	99	1.04	(0.67, 1.61)
Undifferentiated	35	52.9	10	25	1.44	(0.67, 3.08)

[1]Adjusted for age (continuous), study center (MA, NH), primary relative with breast or ovarian cancer (yes, no), BMI (continuous), parity (0, ≥1), OC use (<3 months, ≥3 months) and tubal ligation (ever, never).

consistency of the association appear to be satisfied. A summary odds ratio of 1.36 suggests that between 10 and 11% of ovarian cancers in these populations are attributable to the genital use of talc depending upon whether the average control exposure of 36% or average case exposure of 43% is considered.

Despite the consistency noted above, the relatively weak odds ratios observed could reflect potential biases, especially recall and confounding. Recall bias is possible because talc exposure in these studies is based on personal recollection. However, recall bias seems more likely to affect exposures that have occurred over a short term than those that have occurred over a long term. Since average duration of talc use exceeded 20 years in both cases and controls in our current study, genital talc exposure may be less likely to be subject to recall bias. Furthermore, if publicity regarding the association correlated with selective recall, one might expect a trend for cases from more recent studies to report higher

Risk of ovarian cancer with perineal exposure to talc from key epidemiologic studies.

Odds ratios and confidence intervals

Author	Cases Total n	Cases Exposed (%)	Controls Total n	Controls Exposed (%)	Crude OR (95% CI)
Cramer *et al.* (1982)	215	(42.8)	215	(28.4)	1.9 (1.3-2.8)
Hartge *et al.* (1983)	135	(49.6)	171	(58.5)	0.7 (0.4-1.1)
Whittemore *et al.* (1988)	188	(52.1)	539	(46.0)	1.3 (0.9-1.8)
Harlow and Weiss (1989)	116	(42.2)	158	(40.5)	1.1 (0.7-1.7)
Booth *et al.* (1989)	217	(65.0)	434	(59.0)	1.3 (0.9-1.8)
Harlow *et al.* (1992)	235	(48.5)	239	(39.3)	1.4 (1.0-2.1)
Rosenblatt *et al.* (1992)	77	(87.0)	46	(88.0)	1.0 (0.3-3.0)
Chen *et al.* (1992)	112	(6.2)	224	(2.2)	2.9 (0.9-9.4)
Tzonou *et al.* (1993)	189	(3.2)	200	(3.5)	0.9 (0.3-2.7)
Purdie *et al.* (1995)	824	(56.7)	860	(52.0)	1.2 (1.0-1.5)
Shushan *et al.* (1996)	200	(10.5)	408	(5.6)	2.0 (1.0-3.6)
Cook *et al.* (1997)	313	(50.8)	422	(39.3)	1.6 (1.2-2.1)
Chang and Rish (1997)	450	(44.0)	564	(35.6)	1.4 (1.1-1.8)
Cramer *et al.* (1999)	563	(27.0)	528	(18.2)	1.7 (1.2-2.2)
Summary odds ratio (95% confidence interval)					1.4 (1.2-1.5)

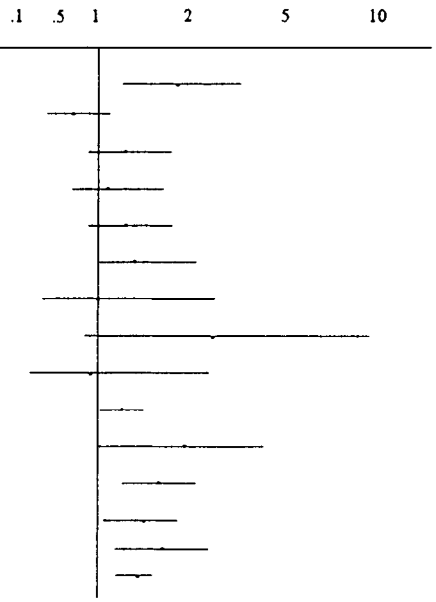

FIGURE 1 – Exposure rates, crude odds ratios and confidence intervals for case-control studies of genital talc use and ovarian cancer.

exposure rates, but the exposure rates noted in Figure 1 do not suggest this is the case. It also seems reasonable that selective recall would lead to cases reporting all types of talc exposure more frequently than controls, but our study found that cases did not report a significant excess of talc use in non-genital areas compared to controls. Finally, if recall accounted for the association, one would expect little variation in the odds ratios by histologic type of ovarian cancer which appears not to be the case from Table V. Our study found the greatest risk to be associated with invasive serous tumors, OR=1.70 (1.22 and 2.39). Cook *et al.* (1997) found talc use to be most strongly associated with serous and unclassified cancers, although Chang and Risch (1997) found endometrioid cancers to be more strongly linked with talc use.

Regarding potential bias from confounding, we found no evidence that genital talc exposure varied by key risk factors for ovarian cancer such as age, parity or OC use and little variability of the association by these and other variables (Table II). Chang and Risch (1997) adjusted for age, parity, breastfeeding, oral contraceptive use, tubal ligation or hysterectomy and family history and also found the association to persist. Characteristics such as body odor or excessive perspiration might represent subtle constitutional features that might predispose to both talc use and ovarian cancer, but adjusting for BMI should control for these effects. In addition, 2 previous studies (Cook *et al.*, 1997; Chang and Risch, 1997), and our current study found no evidence of elevated risk associated with genital use of a cornstarch based-powder, although in all of these studies the exposure was infrequent and the OR and confidence interval was wide. Further studies would be valuable since this observation suggests that type of powder used may be more important than underlying reason for use.

The most obvious weakness in the argument for biologic credibility of the talc and ovarian cancer association is the lack of a clear dose response. Most talc and ovarian cancer studies that have addressed dose response, including this one, have failed to demonstrate consistent dose response relationships with measures of the intensity of the exposure, especially when the trend is examined among users only. In attempting to address this weakness, we point out that it is difficult to quantify the amount of powder actually used and degree of perineal dusting that might constitute an "application of talc." Another factor that may affect the dose-response relationship is whether use occurred at a time when the female tract was open. There is evidence from several studies that the talc/ovarian cancer association is modified by closure of the female tract as a result of tubal ligation or hysterectomy (Harlow *et al.*, 1992; Chang and Risch, 1997; Green *et al.*, 1997). We have also proposed that talc use during periods of ovulation may carry greater risk, based on the hypothesis that ovarian surface epithelial disruption and repair accompanying ovulation might allow talc to become entrapped within the inclusion cysts that form with ovulation.

Our current study also suggests that a term pregnancy may affect the relationship between talc and ovarian cancer in a manner that may be independent of ovulation. We observed that the association between talc and ovarian cancer was more apparent in women who used talc prior to a first liveborn pregnancy compared to those who used it only after a first liveborn pregnancy. This may suggest that ovarian tissue that has not (yet) gone through a pregnancy may be more susceptible to talc-induced damage than tissue that has undergone a pregnancy. A possible biologic explanation for this may involve an ovarian change, known as decidual reaction, that occurs during pregnancy. The decidual reaction refers to differentiation of stromal cells that occurs primarily in the endometrium of the pregnant uterus but which also may be seen in the fallopian tubes, pelvic peritoneum and ovarian surface (Herr *et al.*, 1978). Studies to determine whether the decidual reaction alters the susceptibility of ovaries (or pelvic peritoneum) to talc-induced damage may be informative.

Although we do not know precisely how use of talc in the genital area might induce ovarian cancer, some key elements supporting the biologic plausibility of the association have been established. It has been demonstrated that inert particles contaminating the vagina can reach the ovaries (Venter and Iturralde, 1979). Talc has been found in both normal and malignant ovarian tissue (Henderson *et al.*, 1979), although Heller *et al.* (1996) reported a poor correlation between the amount of talc in the ovaries and personal history of talc use. The patency of the female tract and the nature of ovarian cancer as a surface epithelial (mesothelial) lesion make the ovary a target for foreign body carcinogenesis. Indeed, human ovarian cancer has been demonstrated to be a consequence of occupational asbestos exposure (Keal, 1960). Talc, as a chemical relative of asbestos, appears able to induce histologic changes that are similar to those of asbestos, at least in the lungs (Kleinfeld et al., 1967). Biologic credibility for an association would be strengthened by an animal model, but an experiment capturing all of the potential factors in the human "model" would be very difficult. These elements include chronicity of the exposure, anatomic and physiologic uniqueness of women, effects of pregnancy and potential spread through coitus (as suggested by our finding related to ovarian cancer risk associated with a husband's use of talc). Rodent models seem poorly suited to address these issues because of their infrequent ovulation and the fact that the rodent ovary is encased in a bursal sac.

In summary, we have demonstrated a consistent association between talc and ovarian cancer that appears unlikely to be explained by recall or confounding. The dose-response relationship is weak but improved by considering factors such as closure of the female tract, ovulation and exposure prior to pregnancy, and we have outlined a plausible biologic rationale for this association. We estimate that avoidance of talc in genital hygiene might reduce the occurrence of a highly lethal form of cancer by at least 10%. Balanced against what are primarily aesthetic reasons for using talc in genital hygiene, the risk benefit decision is not complex. Appropriate warnings should be provided to women about the potential risks of regular use of talc in the genital area.

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Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer

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Chronic inflammation has been proposed as the possible causal mechanism that explains the observed association between certain risk factors, such as the use of talcum powder (talc) in the pelvic region and epithelial ovarian cancer. To address this issue we evaluated the potential role of chronic local ovarian inflammation in the development of the major subtypes of epithelial ovarian cancer. Factors potentially linked to ovarian inflammation were examined in an Australia-wide case–control study comprising 1,576 women with invasive and low malignant potential (LMP) ovarian tumours and 1,509 population-based controls. We confirmed a statistically significant increase in ovarian cancer risk associated with use of talc in the pelvic region (adjusted odds ratio 1.17, 95% CI: 1.01–1.36) that was strongest for the serous and endometrioid subtypes although the latter was not statistically significant (adjusted odds ratios 1.21, 95% CI 1.03–1.44 and 1.18, 95% CI 0.81–1.70, respectively). Other factors potentially associated with ovarian inflammation (pelvic inflammatory disease, human papilloma virus infection and mumps) were not associated with risk but, like others, we found an increased risk of endometrioid and clear cell ovarian cancer only among women with a history of endometriosis. Regular use of aspirin and other nonsteroidal anti-inflammatory drugs was inversely associated with risk of LMP mucinous ovarian tumours only. We conclude that on balance chronic inflammation does not play a major role in the development of ovarian cancer.
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Key words: ovarian cancer; chronic inflammation; talcum powder

Chronic inflammation (hereafter referred to as inflammation) was first invoked as a possible mechanism leading to the development of epithelial ovarian cancer to explain observed associations between certain factors, such as use of talcum powder in the perineal region or pelvic inflammatory disease (PID) and risk of ovarian cancer.[1] The major mechanisms thought to underlie ovarian carcinogenesis, namely increased pituitary gonadotropins or incessant ovulation, do not explain such associations.

A link between inflammation and cancer in general has long been recognized. As early as 1863, Virchow noticed the presence of leukocytes in cancer tissues and suggested a possible connection between inflammation and cancer.[2] Since inflammation also represents the process by which the immune system responds to infection or irritation, however, it has been referred to as a 'double-edged sword' with acute (beneficial) inflammation distinguished from the chronic (detrimental) inflammation that may prevent a robust anti-tumour response.[3]

Indeed the most consistent evidence linking inflammation with ovarian cancer comes from the many reports that use of talc in the perineal region increases ovarian cancer risk.[4,5] It has been suggested that the association between talc use and ovarian cancer is strongest for serous tumours when compared to other less common subtypes.[4,6,7] This would be consistent with the histological similarities observed between serous ovarian cancer and mesothelioma, which is known to be caused by asbestos, and the shared

Abbreviations: ACS, Australian Cancer Study; AOCS, Australian Ovarian Cancer Study; BMI, body mass index; HPV, human papilloma virus; LMP, low malignant potential; NSAIDs, non-steroidal anti-inflammatory drugs; OC, oral contraceptive; PID, pelvic inflammatory disease; STI, sexually transmitted infection.

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chemical properties of talcum powder and asbestos. Testing various factors that are possibly related to ovarian inflammation in a case–control study, Ness *et al.*[8] found that perineal talc use and endometriosis, defined as the presence of endometrial tissue outside the uterus and associated with localised inflammation at the site of endometriotic implants, were positively associated with ovarian cancer risk. However, they saw no association with PID, which they had also expected to be associated with increased risk.[8] Extending these epidemiological analyses, McSorley *et al.*[9] recently found significantly higher circulating C-reactive protein (CRP) levels, a marker of systemic chronic inflammation, among 167 women with incident ovarian cancer risk in a multicentre nested case–control study.

The potential role of ovarian inflammation in the development of ovarian cancer remains an open question. The aim of the current study was to further examine the role of local chronic inflammation in the development of epithelial ovarian cancer overall and by histologic subtype. In addition to talcum powder use, we examined medical conditions that cause inflammation in the pelvic region, including endometriosis and PID, and we also tested the hypothesis that if inflammation causes ovarian cancer then regular use of anti-inflammatory drugs should be inversely associated with this disease.

Material and methods

Study design

The Australian Ovarian Cancer Study is an Australia-wide population-based case–control study of epithelial ovarian cancer. It includes incident cases of invasive and low malignant potential (LMP) ovarian cancer diagnosed in women (aged 18–79 years) between January 2002 and June 2005. A total of 3,553 women were identified with suspected ovarian cancer. Of these, 304 died before contact could be made, physicians refused to give consent to contact 133, usually because they were too sick or unable to give informed consent and 194 women could not be contacted. A further 167 (5%) were excluded on the basis of language difficulties (70), mental incapacity (33) and illness (64). The remaining 2,755 women were invited to participate and, of these, 2,319 (84% of those approached) agreed to take part.

Two researchers independently abstracted information on tumour site, histological subtype and tumour behaviour (invasive *vs.* LMP) from the diagnostic histopathology reports and discrepancies were resolved by consensus. For a sample of 87 women, the pathology reports and full set of diagnostic slides were reviewed by a gynaecologic pathologist and the agreement with the original abstracted data was more than 97% for tumour site, behaviour and subtype. After histopathology review, 624 women were excluded because they were found to have nonepithelial, nonovarian or benign tumours and 10 because their cancer was first diagnosed before the start of the study period. Of the final 1,685 eligible participants with invasive or LMP cancers of the ovary, peritoneum or fallopian tube, 1,576 (94%) returned a questionnaire and comprised the case population in the current study. Separate analyses were also carried out for the 994 serous, 191 mucinous, 141 endometrioid and 88 clear cell tumours (the remaining 162 tumours were of other epithelial or mixed subtypes).

Potential control participants were identified from the Australian Electoral Roll (all citizens are required by law to enrol). Controls were frequency-matched to the entire case series based on age (5-year groups) and state of residence. In all, 3,600 women were contacted. Of these, 158 were ineligible because of language difficulties ($n = 97$) or illness ($n = 61$) and 16 were unable to be contacted a second time. Of the 3,426 eligible women, 1,612 (47%) agreed to participate and returned a questionnaire. From these women, 6 were excluded because they reported a previous ovarian cancer and 97 because of a previous bilateral oophorectomy resulting in a total of 1,509 controls for study.

Study participants filled in a comprehensive health and lifestyle questionnaire, which included questions about their personal details, physical characteristics, family history, medical and surgical history, lifestyle habits and reproductive factors. To determine use of talcum powder in the perineal region, participants were asked whether they had ever used powder or talc in the genital area or on underwear or sanitary pads/diaphragm. They were asked their age at first use and years of talc use in these areas. Duration of talcum powder use prior to and after hysterectomy/tubal ligation was calculated and in all analyses perineal talc use was defined as use occurring while the reproductive tract was patent (*i.e.*, prior to hysterectomy/tubal ligation for those women who had undergone gynaecological surgery). Information on talc use under the arms or on the chest or abdomen was also collected.

To measure use of nonprescription anti-inflammatory medications, participants were given examples of the type of medication (*e.g.*, aspirin) followed by a list of the common generic and brand names. To quantify the frequency of use, participants were asked how often they had taken various medications over the past 5 years (ranging from never to as much as twice or more per day). The current analyses were restricted to medications known to suppress inflammation namely aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs). Participants were also asked whether they had ever had any of a number of specific medical conditions and, if so, the ages at which these were diagnosed.

Ethics approval was received from the Human Research Ethics Committees at the Queensland Institute of Medical Research, Peter MacCallum Cancer Centre, University of Melbourne, all participating hospitals and cancer registries.

Statistical analysis

Risk estimates were calculated as odds ratios (OR) with 95% confidence intervals (CI). χ^2-Squared tests were used to test for differences in patient characteristics (*e.g.*, age, level of education). All significance tests were 2-sided and a p-value of less than 0.05 was taken as significant. Unconditional multiple logistic regression models were constructed to simultaneously adjust for confounding factors.

Exposures to factors of interest occurring in the 12 months prior to diagnosis for cases (or 12 months prior to first contact for controls) were excluded because the aetiological influence of very recent exposures on incident ovarian cancer is likely to be minimal and, in cases, recent behaviours may reflect the presence of subclinical disease. All models were adjusted for the categorical variables of age in 10-year groups (<50, 50–59, 60–69, ≥ 70), highest level of education, parity (number of pregnancies >6 months) and duration of contraceptive use (including oral contraceptive pills and contraceptive injections). Analyses of endometriosis and potential symptoms of endometriosis (painful or long periods) were also adjusted for the categorical variable of body mass index (BMI) 1 year prior to diagnosis/recruitment (≤ 24.9, 25–29.9, ≥ 30 kg/m^2). Other potential confounders that were considered for all analyses but not included in the final models since they did not substantially alter risk estimates were: income, family history of ovarian or breast cancer, hysterectomy and/or tubal ligation and smoking.

All analyses were performed using the SAS system V 9.1 (SAS Institute, Cary, NC). Tests for linear trend were performed using the maximum likelihood test with the categorical variable of interest entered as a continuous term.

Results

The final study population included 1,576 women with epithelial ovarian cancer (invasive and LMP) and 1,509 controls. Cases were significantly older than controls (mean age cases = 57.8, mean age controls = 56.42, $p = 0.001$) and were less likely to have continued their education beyond high school (Table I). As expected, cases were significantly more likely to be nulliparous

TABLE I – DESCRIPTIVE CHARACTERISTICS OF 1,576 WOMEN WITH EPITHELIAL OVARIAN CANCER AND 1,509 RANDOMLY SELECTED POPULATION-BASED CONTROLS

Variable	Controls[1] (N = 1,509) N (%)	Cases[1] (N = 1,576) N (%)	p-Value
Highest level of education			
High school	735 (49)	851 (54)	0.02[2]
Technical college/ trade certificate	550 (37)	502 (32)	
University	218 (15)	214 (14)	
Number pregnancies (≥6 months)			
Nulliparous	181 (12)	298 (19)	<0.0001[3]
1–2	644 (43)	647 (41)	
≥3	684 (45)	628 (40)	
Ever used oral contraceptives			
No	330 (22)	505 (32)	<0.0001[3]
≤5 years	361 (24)	432 (28)	
>5 years	811 (54)	619 (40)	
Previous tubal ligation	406 (27)	355 (23)	0.0003[2]
Previous hysterectomy	289 (19)	364 (23)	0.05[2]
Mother/sister with ovarian or breast cancer	195 (13)	273 (19)	0.002[2]

[1]Numbers may not sum to total because of missing data.–[2]χ^2-square test for heterogeneity, adjusted for age group (10 year categories).–[3]χ^2-square test for trend, adjusted for age group (10 year categories).

and to report a mother or sister with ovarian or breast cancer. Cases were less likely to have used oral contraceptives or to report a previous tubal ligation. Unexpectedly, cases were somewhat more likely to report a prior hysterectomy (Table I).

Ever use of talc in the perineal region (among women with patent fallopian tubes) was associated with a significant increase in risk of all types of epithelial ovarian cancer combined (adjusted OR = 1.17, 95% CI: 1.01–1.36) (Table II). Analysis by histological subtype showed that the increase in risk was strongest for serous and endometrioid tumours although it was only statistically significant for serous tumours (adjusted OR = 1.21, 95% CI: 1.03–1.44 and 1.18, 95% CI 0.81–1.70, respectively). This increased risk was seen for both invasive and LMP serous tumours (data not shown), although the association with LMP tumours was not statistically significant because of the smaller numbers. There was no clear trend of increasing risk with longer duration of use, although tests for trend were of borderline statistical significance for all cancers and the serous subgroup (p = 0.02 for both). When we considered invasive and LMP tumours separately, a modest but statistically significant increase in risk of invasive serous tumours was observed in the highest category of use (over 25 years, adjusted OR = 1.35, 95% CI: 1.06–1.72), whereas little or no increased risk was observed with less than 25 years of use. For serous LMP tumours, a modest increase in risk was observed only in the lowest duration of use category (upto 10 years, adjusted OR = 1.71, 95% CI: 1.07–2.73) with no association for over 10 years of use.

Increased risk of ovarian cancer was specifically related to talc use in the pelvic region as talc use on other body sites showed no association (OR = 1.01, 95% CI: 0.84–1.20). In contrast to the elevated risk of ovarian cancer observed with perineal talc use prior to hysterectomy and/or tubal ligation, talc use after such surgery showed no association with serous ovarian cancer risk, regardless of duration (Table II).

Prior to 1976, talcum powder was often contaminated with asbestos fibres.[10,11] To assess whether the association between use of talc and ovarian cancer risk varied over time we evaluated this separately for different age groups. Our assumption was that use of talcum powder among older women would largely have been prior to 1976 (when voluntary guidelines to prevent asbestos contamination of talcum powder were adopted) whereas a greater pro-

TABLE II – ASSOCIATION BETWEEN PERINEAL TALCUM POWDER USE (SEPARATING THE EFFECTS OF USE PRIOR TO AND AFTER HYSTERECTOMY AND/OR TUBAL LIGATION) AND RISK OF EPITHELIAL OVARIAN CANCER

	Controls[1] N (%)	All cases[1] N (%)	All cases (N = 1,576) OR[2] (95% CI)	Serous (N = 994) OR[2] (95% CI)	Mucinous (N = 191) OR[2] (95% CI)	Endometrioid (N = 141) OR[2] (95% CI)	Clear cell (N = 88) OR[2] (95% CI)
Perineal use of talcum powder[3]							
Never	835 (57)	821 (54)	1.0	1.0	1.0	1.0	1.0
Ever	635 (43)	702 (46)	1.17 (1.01–1.36)	1.21 (1.03–1.44)	1.10 (0.80–1.52)	1.18 (0.81–1.70)	1.08 (0.68–1.72)
Use pre- or no-surgery[3]							
None	835 (57)	821 (54)	1.0	1.0	1.0	1.0	1.0
>0–10 years	193 (13)	200 (13)	1.13 (0.90–1.41)	1.26 (0.98–1.63)	0.79 (0.47–1.33)	1.05 (0.59–1.85)	1.08 (0.52–2.27)
>10–25 years	214 (15)	213 (14)	1.08 (0.87–1.34)	1.03 (0.80–1.32)	1.34 (0.86–2.08)	1.14 (0.67–1.94)	0.96 (0.48–1.90)
>25 years	228 (16)	289 (19)	1.29 (1.04–1.58)	1.34 (1.06–1.68)	1.21 (0.75–1.97)	1.31 (0.80–2.16)	1.18 (0.63–2.22)
p-Value (trend)			*0.021*	*0.022*	*0.27*	*0.28*	*0.69*
Use post-surgery							
None	1,294 (88)	1,340 (88)	1.0	1.0	1.0	1.0	1.0
>0–10 years	49 (3)	50 (3)	1.08 (0.71–1.62)	1.07 (0.67–1.69)	1.39 (0.60–3.19)	0.97 (0.34–2.77)	0.64 (0.15–2.81)
>10–25 years	81 (6)	87 (6)	1.14 (0.82–1.57)	1.03 (0.72–1.48)	2.04 (1.09–3.79)	1.03 (0.45–2.32)	0.44 (0.11–1.88)
>25 years	46 (3)	46 (3)	1.00 (0.64–1.51)	1.09 (0.69–1.71)	0.91 (0.27–3.05)	0.79 (0.23–2.64)	0.43 (0.06–3.22)
p-Value (trend)			*0.61*	*0.60*	*0.12*	*0.81*	*0.16*
Ever[3] vs. never use stratified by age at diagnosis/recruitment							
<50 years	143 (23)	137 (20)	1.16 (0.86–1.57)	1.53 (1.06–2.19)	1.42 (0.89–2.25)	0.66 (0.28–1.55)	0.98 (0.41–2.29)
50–59 years	213 (33)	237 (34)	1.22 (0.93–1.59)	1.20 (0.89–1.62)	0.76 (0.46–1.26)	1.41 (0.78–2.54)	1.67 (0.88–3.15)
60–69 years	191 (30)	207 (29)	0.93 (0.70–1.23)	0.95 (0.70–1.29)	0.83 (0.49–1.40)	1.31 (0.62–2.75)	0.87 (0.40–1.85)
≥70 years	88 (14)	121 (17)	1.61 (1.10–2.36)	1.66 (1.08–2.56)	0.91 (0.42–1.97)	1.32 (0.50–3.49)	1.41 (0.58–3.35)

[1]Numbers may not sum to total because of missing data.–[2]Adjusted for age (except age-stratified analysis), education, parity and oral contraceptive pill use.–[3]Analysis restricted to use while the genital tract was unobstructed (i.e., prior to hysterectomy).

portion of use in younger women would have been after that date. Significantly elevated risks of ovarian cancer overall and for the serous subtype were seen in women who were 70 years of age or older and also among those who were less than 50 for the serous subtype only. A modest increase in risk was also observed in the 50–59 year group (nonsignificant) however no association was observed in the 60–69 year age group. Similar results were observed when invasive tumours were examined separately (the number of LMP tumours was too small to evaluate the effects by age).

Table III shows no significant association was observed between PID and risk of all subtypes of ovarian cancer combined (OR = 1.15, 95% CI: 0.85–1.57), or for the different histological subtypes. When we examined the association relative to the time elapsed since diagnosis of PID, no association with ovarian cancer risk was observed (data not shown).

A reported history of genital herpes was not associated with risk of all subtypes of ovarian cancer combined (OR = 1.17, 95% CI: 0.73–1.87). However, a significant positive association was seen with risk of serous tumours (OR = 1.65, 95% CI: 1.01–2.69; Table III), with similar nonsignificant increases observed for both invasive (OR = 1.65, 95% CI: 0.98–2.78) and LMP serous tumours (OR = 1.76, 95% CI: 0.71–4.34). For serous tumours, similar increased risks were seen for both more recent (less than 20 years) and long-term (over 20 years) infection (data not shown).

Neither HPV infection, based on self-reported history of abnormal pap smears and/or genital warts, nor a history of mumps after the age of puberty were associated with risk of ovarian cancer overall (Table III). There was also no association with mumps when we considered infection at any age (OR = 0.95, 95% CI: 0.81–1.12). There was however a suggestion that HPV infection was associated with a slightly increased risk of the endometrioid subtype (OR = 1.58, 95% CI: 1.03–2.44). Analyses considering time since the condition was first reported did not alter these results.

We found no significant association between a reported history of endometriosis and ovarian cancer risk overall (OR = 1.31, 95% CI: 0.97–1.78). However statistically significant increased risks were seen for the endometrioid and clear cell subtypes (OR = 1.85, CI: 1.02–3.38 and OR = 2.66, CI: 1.31–5.44, respectively). Because endometriosis may go undiagnosed, we also considered a reported history of potential symptoms of endometriosis (long or painful periods) however neither was associated with ovarian cancer risk (Table III). Similar results were noted when the analysis was restricted to women who had not used hormonal contraceptives. As with other medical conditions, risk estimates did not vary with time elapsed since endometriosis was first reported.

For comparison with inflammation believed to occur in close proximity to the ovaries, medical conditions associated with inflammation at other body sites were also examined (including gall stones, inflammatory bowel disease, diverticulitis, oesophagitis, gastritis and pancreatitis). None of these conditions was associated with ovarian cancer risk (data not shown).

To assess whether regular use of anti-inflammatory medications was inversely associated with ovarian cancer risk, use of aspirin and NSAIDs in the 5 years prior to study recruitment was examined. Any use of aspirin was not associated with ovarian cancer risk for all subtypes combined (OR for any *vs.* no use = 1.06, 95% CI: 0.92 1.23; Table IV) or for any of the individual subtypes. Ever use of NSAIDs in the last 5 years also had no effect on risk of all subtypes of ovarian cancer (OR = 0.88, 95% CI: 0.76–1.02). However, risk of mucinous tumours was inversely associated with any use of NSAIDs (OR = 0.69, 95% CI: 0.50–0.94) and a further decrease in risk was observed with more frequent use (p-value trend = 0.01). Separate analyses of invasive (n = 44) and LMP (n = 147) mucinous tumours demonstrated that the observed inverse association was driven entirely by LMP tumours (OR for any *vs.* no use = 0.59, 95% CI: 0.41–0.84, compared to

TABLE III – ASSOCIATION BETWEEN SELF-REPORTED MEDICAL CONDITIONS POTENTIALLY ASSOCIATED WITH INFLAMMATION OF THE OVARIES AND RISK OF EPITHELIAL OVARIAN CANCER

	Controls[1] N (%)	All cases[1] N (%)	All cases (N = 1,576) OR[2] (95% CI)	Serous (N = 994) OR[2] (95% CI)	Mucinous (N = 191) OR[2] (95% CI)	Endometrioid (N = 141) OR[2] (95% CI)	Clear cell (N = 88) OR[2] (95% CI)
PID							
Never	1,406 (94)	1,460 (93)	1.0	1.0	1.0	1.0	1.0
Ever	84 (6)	103 (7)	1.15 (0.85–1.57)	0.96 (0.66–1.38)	1.46 (0.82–2.60)	1.29 (0.66–2.52)	0.87 (0.30–2.49)
Genital herpes							
Never	1,420 (98)	1,425 (97)	1.0	1.0	1.0	1.0	1.0
Ever	35 (2)	42 (3)	1.17 (0.73–1.87)	1.65 (1.01–2.69)	0.40 (0.09–1.71)	0.32 (0.04–2.37)	0.74 (0.10–5.63)
HPV infection							
Never	1,148 (78)	1,197 (81)	1.0	1.0	1.0	1.0	1.0
Ever	317 (22)	273 (19)	0.94 (0.78–1.15)	0.92 (0.74–1.15)	0.98 (0.66–1.45)	1.58 (1.03–2.44)	0.72 (0.36–1.47)
Mumps							
Never	496 (76)	508 (75)	1.0	1.0	1.0	1.0	1.0
Ever (postpubertal)	160 (24)	164 (25)	0.96 (0.73–1.25)	1.06 (0.79–1.42)	0.78 (0.40–1.49)	0.97 (0.50–1.87)	0.81 (0.35–1.92)
Endometriosis[3]							
Never	1,413 (94)	1,431 (92)	1.0	1.0	1.0	1.0	1.0
Ever	87 (6)	124 (8)	1.31 (0.97–1.78)	1.14 (0.80–1.62)	0.89 (0.46–1.75)	1.85 (1.02–3.38)	2.66 (1.31–5.44)
Long periods[3] (>7 days)							
Never/rarely	1,174 (82)	1,173 (82)	1.0	1.0	1.0	1.0	1.0
Often	188 (13)	192 (14)	1.05 (0.83–1.31)	1.05 (0.81–1.36)	0.70 (0.40–1.22)	1.23 (0.71–2.12)	1.26 (0.62–2.53)
Always	75 (5)	62 (4)	0.79 (0.55–1.13)	0.82 (0.55–1.23)	0.78 (0.34–1.78)	0.72 (0.27–1.85)	0.83 (0.24–2.83)
Painful periods[3]							
Never/rarely	760 (52)	711 (49)	1.0	1.0	1.0	1.0	1.0
Sometimes	290 (20)	301 (20)	1.04 (0.85–1.27)	1.04 (0.83–1.31)	0.95 (0.61–1.47)	1.07 (0.65–1.75)	1.13 (0.59–2.15)
Often	404 (28)	452 (31)	1.17 (0.98–1.40)	1.17 (0.96–1.43)	1.12 (0.77–1.64)	1.12 (0.72–1.73)	1.14 (0.65–2.00)

[1]Numbers may not sum to total because of missing data.–[2]Adjusted for age, education, parity and oral contraceptive pill use.–[3]Additionally adjusted for body mass index one year prior to diagnosis.

TABLE IV – ASSOCIATION BETWEEN ANTI-INFLAMMATORY MEDICATION USE IN THE PAST 5 YEARS AND RISK OF EPITHELIAL OVARIAN CANCER

	Controls[1] N (%)	All cases[1] N (%)	All cases (N = 1,576) OR[2] (95% CI)	Serous (N = 994) OR[2] (95% CI)	Mucinous (N = 191) OR[2] (95% CI)	Endometrioid (N = 141) OR[2] (95% CI)	Clear cell (N = 88) OR[2] (95% CI)
Aspirin							
Never	772 (51)	783 (50)	1.0	1.0	1.0	1.0	1.0
Ever	730 (49)	781 (49)	1.06 (0.92–1.23)	1.06 (0.90–1.25)	0.99 (0.72–1.35)	0.92 (0.64–1.32)	0.92 (0.58–1.45)
≤1/week	612 (41)	650 (41)	1.06 (0.91–1.23)	1.05 (0.88–1.25)	0.98 (0.71–1.36)	0.98 (0.68–1.43)	0.95 (0.59–1.54)
≥2/week	118 (8)	131 (8)	1.06 (0.80–1.41)	1.11 (0.81–1.51)	1.02 (0.52–2.03)	0.56 (0.23–1.34)	0.75 (0.30–1.89)
p-Value (trend)			*0.5*	*0.4*	*0.99*	*0.4*	*0.6*
NSAIDs							
Never	625 (42)	723 (46)	1.0	1.0	1.0	1.0	1.0
Ever	878 (58)	836 (54)	0.88 (0.76–1.02)	0.93 (0.78–1.10)	0.69 (0.50–0.94)	0.76 (0.53–1.09)	0.92 (0.58–1.45)
≤1/week	653 (43)	625 (40)	0.90 (0.76–1.05)	0.94 (0.78–1.12)	0.73 (0.53–1.02)	0.73 (0.50–1.09)	0.97 (0.59–1.60)
≥2/week	225 (15)	211 (14)	0.83 (0.66–1.04)	0.90 (0.70–1.16)	0.51 (0.28–0.93)	0.84 (0.49–1.44)	0.79 (0.39–1.58)
p-Value (trend)			*0.1*	*0.3*	*0.01*	*0.3*	*0.6*

[1]Numbers may not sum to total because of missing data.–[2]Adjusted for age, education, parity and oral contraceptive pill use.

1.17, 95% CI 0.62–2.21 for invasive mucinous tumours). There was also a dose-response relationship for LMP mucinous tumours (OR for 2 or more pills per week *vs.* no use = 0.46, 95% CI: 0.23–0.91, *p*-value trend = 0.01).

Discussion

The hypothesis that chronic inflammation may lead to the development of epithelial ovarian cancer was first proposed to explain how certain factors, such as talc use in the perineal region, may be linked to increased risk of developing ovarian cancer.[1] Testing the inflammation hypothesis in a case–control study, Ness *et al.* found that proinflammatory factors, such as perineal talc use and endometriosis increased ovarian cancer risk, but others such as PID did not significantly increase ovarian cancer risk (separate analyses of individual histological subtypes of ovarian cancer were not presented).[8] Consistent with this hypothesis, McSorley *et al.*[9] recently reported a trend of increasing ovarian cancer risk with increasing levels of CRP, a marker of inflammation. However, given the lack of specificity of CRP and its association with prevalent chronic conditions, such as ischaemic heart disease,[12] it is difficult to rule out confounding as an alternate explanation for these results.[9] Until the present study, no other epidemiological studies appear to have tested the hypothesis that ovarian inflammation is associated with ovarian cancer risk. In the current study, a significantly elevated risk of ovarian cancer overall and of the serous subtype associated with perineal talc use was identified. A nonsignificant increase in risk was also seen for endometrioid tumours. Other factors that could potentially cause ovarian inflammation (such as PID, HPV infection, mumps and endometriosis) were not associated with ovarian cancer risk overall, however there was some evidence of a positive association with some of these factors in the subtype specific analyses. These results in combination with previous studies suggest that chronic inflammation is unlikely to play a major role in the development of ovarian cancer.

Focusing on talc use, we found that any use of perineal talc was associated with a small but significantly increased risk of ovarian cancer overall and specifically amongst the invasive and LMP serous tumours although no clear dose-response with increasing duration of use was identified. This finding is consistent with results of previous studies.[4,6,7,10,13,14]

As expected, ovarian cancer risk was only related to talc use in women with no surgical closure of the fallopian tubes or those who had used talc presurgery, with no association seen for talc use after tubal sterilisation or hysterectomy. Similar observations were made in previous case–control studies of ovarian cancer (all subtypes) with elevated risks observed in women who had not had a tubal ligation[4,14] or those who had used talc presurgery.[13] These former studies together with the current findings support the hypothesis that talc particles are transported to the ovaries *via* unobstructed fallopian tubes. In contrast, the Nurses' Health study found no increase in risk among women who were perineal talc users but had never had a tubal ligation.[7]

While it has been demonstrated experimentally that talc particles can reach the ovaries in humans and rodents as the result of talc use in the pelvic region,[15–17] ovarian talc particle burden in normal human ovaries is not correlated with reported exposure levels.[17] This suggests that use of only a small amount of talc may be required for some talc to reach the ovaries and increase risk of cancer.

It has been hypothesised that talc is linked to ovarian cancer development through inflammation, however evidence linking an inflammatory response with talc contamination of the ovaries is lacking. Talc-induced inflammation is unlikely to be in the formation of granulomas as these are rarely observed in human ovaries.[18,19] Other likely manifestations of talc-induced inflammation include reduced fibrinolysis, activation of neutrophils and macrophages and increased production of cytokines and growth factors, and these have been suggested to occur in the peritoneum in response to contamination by surgical glove powder.[20] Rigorous investigation of the precise biological response of the ovarian surface epithelium to perineal talc use is needed.

We also sought to determine whether possible contamination of talc with asbestos fibres, which are known to cause inflammation of epithelial tissues, could explain the observed link between perineal talc use and serous ovarian cancer. Voluntary guidelines to prevent asbestos contamination of cosmetic talc were introduced in 1976 and consequently earlier formulations were more likely to contain asbestos fibres.[10,11] Increased risk of serous ovarian cancer was not restricted to perineal talc use in the oldest age groups, who were more likely to have been exposed to asbestos-contaminated talc, but was also observed in the youngest (less than 50 years) and the 50–59 year old age group. Other studies have also reported no increase in risk of all subtypes of ovarian cancer associated with talc use before 1970[13] or before 1975.[14] These findings contrast with 2 other reports of increased risk of serous[7] and all subtypes of epithelial ovarian cancer[10] associated with earlier use of talc.

If inflammation plays a role in the aetiology of ovarian cancer then it would be expected that PID would be associated with increased risk of ovarian cancer. PID was not associated with elevated risk of ovarian tumours in our data, confirming several previous reports of no association with PID in studies of all subtypes of ovarian cancer.[8,21,22] To date there has been only one report of a significant positive association between PID and ovarian cancer.[23] Genital herpes infection was associated with a nonsignificant increased risk of invasive serous cancer in our data, although this observation was based on a small number of exposed cases ($n = 27$). One previous study found no association between genital herpes and ovarian cancer risk (the number of exposed cases was not reported).[8] Latent infection by herpes virus is established

in the nerve root ganglia and it is associated with a variety of initial and recurrent symptoms such as genital ulceration.[24] It is biologically plausible that inflammation associated with genital herpes infection could increase risk of ovarian cancer as Herpes simplex virus type 2 has been detected in the upper genital tract of women with acute PID[25,26] and acute salpingitis.[27] Further studies are needed to confirm this association.

HPV infection (based on reports of abnormal pap smears and/ or genital warts) showed no association with ovarian cancer risk, except for the endometrioid subtype. We hypothesised that HPV infection could potentially cause ovarian inflammation as HPV DNA has been identified in the ovaries of patients with primary ovarian squamous intraepithelial neoplasia[28,29] and in the upper genital tract of patients with cervical squamous carcinoma.[30] In addition, high-risk HPV DNA has been reported in 10% of ovarian epithelial carcinomas.[31] Abnormal pap smears and genital warts are generally associated with HPV genotypes classified as high-risk and low-risk, respectively, in regards to their association with carcinogenic transformation.[32] However, separate analyses also showed no association with ovarian cancer risk.

Mumps infection (either after puberty or at any age) was not associated with ovarian cancer risk. It has been estimated that some 5% of postpubertal mumps cases are associated with clinically apparent oophoritis, which in severe cases could result in infertility caused by nonfunctional ovarian tissue.[33] We were unable to identify these particular cases in the current analysis and therefore further study is needed to examine the association between mumps oophoritis and ovarian cancer.

While endometriosis is a condition associated with localised inflammation, it is also related to changes in hormone levels (increased oestrogen unopposed by progesterone) at the site of endometriotic implants.[34] Despite this, endometriosis or potential symptoms of endometriosis (long or painful periods) were not associated with ovarian cancer risk overall, but there was an increased risk of endometrioid and clear cell subtypes among women who reported a history of endometriosis. This result was anticipated because current epidemiological evidence suggests that endometriosis is most strongly associated with the endometrioid and clear cell subtypes of ovarian cancer.[35,36]

Finally, if inflammation did promote epithelial ovarian cancer development, then it may be reasonably expected that regular use of anti-inflammatory medications would reduce risk. However, no overall association with ovarian cancer risk was observed in the current study. This supports results from 2 recent meta-analyses, which have also not shown that regular use of anti-inflammatory medications (aspirin or other NSAIDs) reduces ovarian cancer risk.[37,38] Of interest however was the apparent inverse association between NSAID use and the mucinous subtype, which was entirely driven by the LMP group. We know from other epidemiological studies that the aetiology of mucinous tumours differs in a number of ways from the other subtypes of ovarian cancer, so NSAID use may be another factor to add to this list. However, this result awaits confirmation by others.

Strengths of our study included its large size (1,576 women with ovarian cancer and 1,509 population-based controls) and Australia-wide coverage. A limitation was the low response rate for controls (47%), which could have resulted in selection bias and possibly led to an over-representation of healthy subjects among the controls. Indeed our hysterectomy rate among controls was ~5% lower than expected, but as there are no obvious links between hysterectomy and inflammation that we have not considered, we do not believe that these small differences would have affected the present results. A healthy control bias would most likely influence the analyses of medical conditions, specifically sexually transmitted infections (STIs). For example, if participating controls were less likely to have had an STI this could bias risk estimates for STIs upwards. While we saw a positive association between herpes infection and ovarian cancer risk, there was no association with other STIs suggesting that our ORs are not systematically biased. Overall, a small number of participants reported STIs and it is possible that STIs were underreported because of possible asymptomatic infection or because of the negative connotations associated with having an STI. It is also possible that controls would be more likely to underreport STIs than cases therefore potentially biasing the risk estimates upwards. Another general limitation was that analyses of medical conditions were based entirely on self-reported medical history and as a result the accuracy of these reports could not be confirmed, although self-reports of these miscellaneous conditions are unlikely to be influenced greatly by case/control status.

In summary, most factors that could potentially cause ovarian inflammation (such as PID, HPV infection, and postpubertal mumps) were not associated with a significant elevation in ovarian cancer risk in our study. In addition, the expected corollary, an inverse association with regular use of anti-inflammatory medications, was not observed. While some subtype-specific associations were observed, these were not strong and showed no coherent pattern of association within or across subtypes, aside from the well-recognised increase in risk of endometrioid and clear cell cancers among women with endometriosis. The elevation in ovarian cancer risk associated with use of talc in the perineal region that we and others have observed has been regarded as the main evidence supporting an inflammatory mechanism in the development of epithelial ovarian cancer. However, experimental evidence that perineal talc use elicits an inflammatory response in the ovaries is lacking and overall we conclude that chronic inflammation does not play a major role in the development of ovarian cancer.

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ORIGINAL PAPER

Genital powder exposure and the risk of epithelial ovarian cancer

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Abstract
Background We conducted a population-based, case–control study to examine the association between the use of genital powder and ovarian cancer risk, including measures of extent and timing of exposure. We also assessed the relationship of powder use with risk of disease subtypes according to histology and degree of malignancy.
Methods Information was collected during in-person interviews with 812 women with epithelial ovarian cancer diagnosed in western Washington State from 2002 to 2005 and 1,313 controls. Logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs).
Results Overall, the perineal use of powder after bathing was associated with a slightly increased ovarian cancer risk (OR = 1.27, 95% CI: 0.97–1.66), which was most evident among women with borderline tumors (OR = 1.55, 95% CI: 1.02–2.37). We noted no clear pattern of risk increase on the basis of the extent of use, assessed as years in which powder was used, or as lifetime number of applications for invasive or borderline tumors, or their histologic subtypes. There was no alteration in the risk of ovarian cancer associated with other types of powder exposure (e.g., on sanitary napkins or diaphragms).
Conclusions The International Agency for Research on Cancer has designated perineal exposure to talc (via the application of genital powders) as a possible carcinogen in women. A modest association of ovarian cancer with this exposure was seen in our study and in some previous ones, but that association generally has not been consistent within or among studies. Therefore, no stronger adjective than "possible" appears warranted at this time.

Keywords Ovarian neoplasms · Talc · Epidemiology

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Introduction

Talc deposition in the body can lead to inflammatory and neoplastic changes [1], and perineal exposure to certain particulates (conceivably, talc) can lead to their deposition in the peritoneal cavity and ovaries [2]. Multiple case–control studies [3–5] and one cohort study [6] have examined risk of ovarian cancer associated with perineal exposure to dusting powders (many of which contain talc), either overall or within specific histologic subgroups of disease. In a meta-analysis of 20 case–control studies [3], the summary estimate of the relative risk (RR) of ovarian cancer among women who reported any perineal use of powder was 1.35 (95% confidence interval (CI): 1.26–1.46). Although no association of this exposure with ovarian cancer risk was noted in the cohort study overall, risk of invasive serous cancers was modestly elevated (by 40%). The International Agency for Research on Cancer has classified perineal exposure to talc as group 2B (possibly carcinogenic to humans [3, 7]).

In this article, we describe the results of a large population-based study of epithelial ovarian cancer conducted in western Washington State in which we further investigated the association between the use of genital powder and the

ovarian cancer risk, including measures of extent of use and aspects of timing of exposure. We also assessed the relationship of powder use with risk of disease subtypes according to histology and degree of malignancy.

Materials and methods

The study population and methods have been described previously [8]. Female residents, of a 13 county areas of western Washington State, 35–74 years of age, who were diagnosed with a primary invasive or borderline (also known as low malignant potential or LMP) epithelial ovarian tumor between 1 January 2002 and 31 December 2005, were considered eligible as cases. The cases were identified through a population-based cancer registry, the Cancer Surveillance System, which is part of the Surveillance, Epidemiology, and End Results Program (SEER) of the US National Cancer Institute. We restricted our cases to English-speaking women who had residential telephones at the time of diagnosis, because random digit dialing (RDD) was the method used to select control subjects. Of the 1,058 eligible women identified, 812 (76.6%) were interviewed. Of the interviewed cases, 595 had invasive disease. Tumors were categorized into the following histologic subgroups: serous ($n = 452$), mucinous ($n = 112$), endometrioid ($n = 104$), clear cell ($n = 35$), and other epithelial tumors ($n = 109$).

Controls were selected by RDD using stratified sampling in 5-year age categories, 1-year calendar intervals, and two county strata in a 2:1 ratio to women with invasive cancer. For 14,561 (82.0%) of the 17,768 telephone numbers belonging to residences, we determined whether an eligible woman (i.e., an age and county eligible woman able to communicate in English and, if so, with at least one ovary and no prior history of ovarian cancer) resided there. Of the 1,561 eligible women identified, 1,313 were interviewed (84.1%) for an overall (screening X interview) response proportion of 69%.

The study was approved by the Institutional Review Boards of the Fred Hutchinson Cancer Research Center and the University of Illinois at Urbana Champaign, and all women provided signed informed consent before participating. In-person interviews pertained to the period of time before diagnosis (for cases) or before an assigned comparable reference date (for controls), and covered the following: demographic and lifestyle characteristics; medical history; and detailed reproductive history, including menstrual, pregnancy, and contraceptive history, as well as the use of contraceptive and menopausal hormone preparations. To aid recall, interviewers used a calendar to record major life events and provided photographs of the commonly used oral contraceptive and menopausal hormone preparations.

Several sources of genital powder exposure were assessed in separate questions, including direct perineal application after bathing, its use on sanitary napkins and contraceptive diaphragms, and the use of feminine (vaginal) deodorant spray. For powder use on sanitary napkins and use of feminine deodorant sprays, we recorded the total number of months or years in which these products were used (with a minimum of at least 1 month of regular use). For the use of powder on the perineum after bathing, only intervals of at least 1 year when powder was usually used were recorded. For each reported interval in which powder was usually used on the perineum after bathing, we recorded the age when began and ended, the number of weeks or months of use per year, and the average days per week used. Women were also asked to report the types of powder(s) used after bathing, including talcum, baby, cornstarch, deodorant, body/bath, and other or unknown. The extent of exposure to perineal powder after bathing was assessed as lifetime duration of use (i.e., total number of years in which this exposure occurred), and as the estimated lifetime number of applications (i.e., a measure that incorporated both the duration and frequency of use).

Using unconditional logistic regression, we calculated odds ratios (ORs) and related 95% confidence intervals (CIs) as estimates of the RR of epithelial ovarian cancer associated with various aspects of genital powder use. All the analyses were adjusted for the frequency-matching variables of age (5-year intervals), county of residence (dichotomized as the three urban or the 10 rural/suburban counties in the study), and calendar year of diagnosis/reference date (continuous), as well as number of full-term pregnancies (0, 1, 2, or $\geq$3) ,and duration of hormonal contraception (Never, <6, 6–59, 60–119, or $\geq$120 months). Additional adjustment for other potential confounding variables, including race/ethnicity, education, age at menarche, body mass index (BMI), smoking, alcohol drinking, family history of breast or ovarian cancer, personal history of breast cancer, endometriosis, tubal ligation, hysterectomy, unilateral oophorectomy, and the use of menopausal hormone therapy, produced no important change in the OR estimates. We used polytomous logistic regression to examine risk among subgroups of case women with borderline and invasive tumors and in women with different histologic subtypes of these tumors. Because we had limited facility to separately examine risk of mucinous invasive ovarian cancer owing to its rarity ($n = 23$), we excluded these tumors when examining histologic subtypes of invasive disease; similarly, we limited our examination of histologic subtypes of borderline tumors to serous or mucinous subtypes (excluding 11 women with other, uncommon histologic subtypes of borderline tumors). All the analyses were carried out using the STATA version 10 statistical package (Statacorp LP, College Station, Texas).

Results

Characteristics of cases and controls have previously been described [8, 9]. Approximately 90% of cases and controls were non-Hispanic white women. Cases were less likely than controls to have given birth, and reported a lesser extent of exposure to hormonal forms of contraception. Cases were somewhat more likely than controls to be overweight (BMI 25–<30 kg/m^2) or obese (BMI $\geq$ 30 kg/m^2), and less likely to have graduated from college (results not shown).

The use of powder after bathing (for at least 1 year of regular use, as described above) was reported by approximately 12% of controls (Table 1). Other sources of powder exposure (e.g., on sanitary napkins) and the use of deodorant sprays were reported by a slightly smaller proportion of women, despite the shorter minimum time interval allowed in our assessment of these exposures (see Methods for description). Overall, the perineal use of powder after bathing was associated with a slightly increased risk (OR = 1.27, 95% CI: 0.97–1.66), which was the most evident among women with borderline tumors (OR = 1.55, 95% CI: 1.02–2.37). No clear elevation in risk of borderline or invasive tumors were observed in association with the use of powders on sanitary napkins or contraceptive diaphragms, or with the use of feminine deodorant sprays (Table 1). The most frequently reported category of product used after bathing was baby powder (not shown); few women reported exclusive use of talcum powder or of cornstarch (a product that does not contain talcum powder). Within limits of precision, findings regarding ovarian cancer risk among women who reported the use of talcum powder were similar to those presented for all types of powders combined; e.g., the risk of invasive ovarian cancer among women who reported the use of talcum powder was 1.38 (95% CI: 0.77–2.47).

We noted no evidence that risk of ovarian cancer increased in association with increasing extent of the use of perineal dusting powder (assessed as years in which powder was used or as lifetime number of applications) for either invasive or borderline tumors (Table 2). Similarly, we observed no trend in risk with increasing years of powder use on sanitary napkins or with the use of feminine deodorant sprays (results not shown). Risk (relative to never-users) was increased among women who first reported the regular use of perineal dusting powders at age 30 years or older (OR for invasive and borderline tumors combined = 1.69, 95% CI: 1.08–2.64), among women whose first regular use was in 1980 or later (OR for invasive and borderline tumors combined = 2.03, 95% CI: 1.28–3.24), and among women who had initiated regular use within the last 25 years (cut-off point based on approximate quartiles of exposed controls; OR for invasive and borderline tumors combined = 1.77, 95% CI: 1.12–2.78). Point estimates for each of these exposure subgroups were similar for borderline and invasive tumors (Table 2).

We repeated our analyses after [1] restricting the analysis to the use of perineal powder that occurred before tubal ligation and/or hysterectomy (for women who had undergone those procedures) and [2] restricting it to the use of

Table 1 Risk of epithelial ovarian cancer in relation to various sources of genital powder exposure overall and among women with borderline and invasive tumors

	Controls	Borderline tumors			Invasive tumors			All tumors		
	(n = 1,313)[a]	(n = 217)[a]	OR[b]	95% CI	(n = 595)[a]	OR[b]	95% CI	(n = 812)[a]	OR[b]	95% CI
Used powder after bathing										
No	1,161	184	1.00	Ref.	515	1.00	Ref.	699	1.00	Ref.
Yes	151	33	1.55	1.02–2.37	79	1.17	0.87–1.58	112	1.27	0.97–1.66
Used powder on sanitary napkins										
No	1,197	201	1.00	Ref.	552	1.00	Ref.	753	1.00	Ref.
Yes	109	16	1.03	0.58–1.84	39	0.75	0.51–1.12	55	0.82	0.58–1.16
Used powder on diaphragm[c]										
No	321	44	1.00	Ref.	116	1.00	Ref.	160	1.00	Ref.
Yes	121	9	0.60	0.27–1.33	37	0.77	0.49–1.21	46	0.72	0.48–1.10
Used vaginal deodorant spray										
No	1,185	194	1.00	Ref.	532	1.00	Ref.	726	1.00	Ref.
Yes	125	23	1.20	0.74–1.95	61	1.14	0.81–1.59	84	1.15	0.85–1.56

[a] Numbers in column may not sum to total due to missing values

[b] Adjusted for age, calendar year of diagnosis/reference date, county of residence, number of full-term births, and duration of hormonal contraception

[c] Restricted to diaphragm users

Table 2 Risk of epithelial ovarian cancer in relation to the use of perineal powder after bathing by duration and timing of use, overall and among women with borderline and invasive tumors

	Controls	Borderline tumors			Invasive tumors			All tumors		
	(n = 1,313)[a]	(n = 217)[a]	OR[b]	95% CI	(n = 595)[a]	OR[b]	95% CI	(n = 812)[a]	OR[b]	95% CI
Never used[c]	1,161	184	1.00	Ref.	515	1.0	Ref.	699	1.0	Ref.
Duration of use (years)										
1–9.9	38	9	1.33	0.61–2.87	24	1.42	0.83–2.43	33	1.39	0.85–2.28
10–19.9	35	10	1.97	0.93–4.17	19	1.28	0.71–2.29	29	1.46	0.87–2.45
20–34.9	40	10	1.83	0.88–3.80	20	1.11	0.63–1.95	30	1.28	0.78–2.10
35+	38	4	1.08	0.37–3.15	15	0.86	0.46–1.60	19	0.91	0.51–1.62
Lifetime number of applications										
1–1,599	36	6	1.05	0.42–2.61	20	1.26	0.71–2.25	26	1.21	0.71–2.06
1,600–4,799	37	17	3.11	1.67–5.78	28	1.72	1.03–2.88	45	2.08	1.32–3.27
4,800–9,999	39	6	1.19	0.49–2.92	14	0.78	0.41–1.48	20	0.87	0.50–1.53
10,000+	37	4	0.98	0.34–2.85	14	0.84	0.44–1.59	18	0.87	0.48–1.57
Age at first use (years)[c]										
<15	27	4	0.89	0.30–2.66	8	0.67	0.30–1.53	12	0.74	0.37–1.50
15–<20	36	8	1.46	0.64–3.31	19	1.10	0.61–1.97	27	1.20	0.71–2.03
20–<30	43	12	1.93	0.98–3.80	20	1.04	0.59–1.81	32	1.25	0.77–2.03
30+	45	9	1.68	0.79–3.60	32	1.68	1.04–2.72	41	1.69	1.08–2.64
Age at last use (years)[c]										
<35	33	10	1.54	0.72–3.28	15	0.97	0.51–1.83	25	1.14	0.66–1.97
35–<50	39	15	2.07	1.09–3.93	20	1.15	0.65–2.03	35	1.42	0.88–2.31
50–<60	36	6	1.39	0.56–3.44	19	1.20	0.67–2.15	25	1.25	0.73–2.13
60+	43	2	0.64	0.15–2.74	24	1.30	0.76–2.25	26	1.21	0.72–2.05
Calendar year of first use[c]										
≤1959	39	5	1.47	0.55–3.92	14	0.73	0.38–1.40	19	0.86	0.48–1.53
1960–1969	38	4	0.82	0.28–2.38	20	1.18	0.66–2.09	24	1.10	0.65–1.89
1970–1979	38	11	1.65	0.81–3.37	15	0.91	0.49–1.69	26	1.12	0.66–1.89
1980+	36	33	2.20	1.11–4.34	30	1.97	1.18–3.28	43	2.03	1.28–3.24
Time since first use (years)[c]										
≤25	41	12	1.78	0.89–3.54	30	1.76	1.07–2.89	42	1.77	1.12–2.78
25–<38	41	14	1.98	1.03–3.79	24	1.25	0.73–2.13	38	1.46	0.91–2.32
38–<45	34	3	0.79	0.23–2.69	13	0.88	0.45–1.72	16	0.87	0.47–1.61
45+	35	4	1.30	0.44–3.83	12	0.72	0.36–1.43	16	0.82	0.44–1.52
Time since last use (years)[c]										
Current user	70	12	1.35	0.71–2.59	40	1.28	0.85–1.94	52	1.30	0.89–1.91
≤12	26	9	2.11	0.94–4.77	17	1.59	0.83–3.02	26	1.74	0.98–3.10
13–23	27	7	1.80	0.75–4.34	7	0.55	0.24–1.29	14	0.85	0.44–1.66
24+	28	5	1.22	0.45–3.29	14	1.10	0.56–2.17	19	1.13	0.61–2.08

[a] Numbers in column may not sum to total due to missing values

[b] Adjusted for age, calendar year of diagnosis/reference date, county of residence, number of full-term births, and duration of hormonal contraception

[c] Use defined as regular use after bathing for at least 1 year

powder that occurred at age 15 years or later. Results were generally similar to those that we have presented. Associations with any perineal powder exposure that occurred in women with intact fallopian tubes were slightly reduced in comparison to analyses that included powder use irrespective of the occurrence of tubal ligation or hysterectomy (e.g., ORs among women with intact tubes = 1.23 [95% CI: 0.93–1.64] and 1.44 [95% CI: 0.92–2.24], for all ovarian tumors combined and for borderline tumors, respectively). Associations with any perineal powder used

Table 3 Risk of histologic types of invasive and borderline epithelial ovarian cancer in relation to various sources of genital powder

	Borderline tumors[c]				Invasive tumors[c]					
	Mucinous ($n = 89$)		Serous ($n = 117$)		Serous ($n = 335$)		Endometrioid/Clear ($n = 133$)		Other nonmucinous ($n = 104$)	
	N	OR[a] (95% CI)	N	OR[a] (95% CI)	N	OR[a] (95% CI)	N	OR[a] (95% CI)	N	OR[a] (95% CI)
Used powder after bathing[b]										
No	74	1.0 (Ref.)	100	1.0 (Ref.)	295	1.0 (Ref.)	112	1.0 (Ref.)	87	1.0 (Ref.)
Yes	15	1.78 (0.98–3.23)	17	1.47 (0.84–2.55)	40	1.01 (0.69–1.47)	21	1.53 (0.91–2.57)	17	1.48 (0.85–2.58)
Duration of use[b] (years)										
1–9.9	2	0.71 (0.16–3.10)	7	1.89 (0.80–4.47)	11	1.16 (0.58–2.33)	6	1.42 (0.56–3.57)	6	2.18 (0.88–5.40)
10–19.9	6	3.12 (1.22–7.97)	3	1.10 (0.33–3.70)	11	1.26 (0.62–2.54)	5	1.62 (0.60–4.41)	3	1.16 (0.35–3.92)
20–34.9	5	2.45 (0.92–6.56)	5	1.60 (0.60–4.22)	8	0.76 (0.35–1.66)	5	1.40 (0.52–3.74)	7	2.25 (0.97–5.24)
35+	2	1.26 (0.29–5.51)	2	1.02 (0.24–4.40)	10	0.91 (0.44–1.88)	5	1.85 (0.68–5.05)	0	0.00 (–)
Age at first use (years)[b]										
<15	1	0.56 (0.07–4.27)	3	1.24 (0.36–4.30)	3	0.44 (0.13–1.47)	3	1.20 (0.34–4.24)	2	1.02 (0.23–4.43)
15–<20	5	2.30 (0.84–6.33)	3	1.01 (0.30–3.43)	10	1.01 (0.49–2.08)	7	1.99 (0.83–4.76)	2	0.63 (0.15–2.72)
20–<30	5	2.14 (0.80–5.68)	6	1.69 (0.69–4.15)	10	0.90 (0.44–1.83)	3	0.68 (0.20–2.31)	6	1.82 (0.74–4.47)
30+	4	1.80 (0.61–5.28)	5	1.77 (0.67–4.66)	17	1.45 (0.81–2.59)	8	2.33 (1.03–5.27)	7	2.21 (0.95–5.11)
Calendar year of first use[b]										
≤1959	3	2.08 (0.59–7.30)	2	1.07 (0.25–4.70)	6	0.50 (0.20–1.20)	5	1.78 (0.64–4.95)	3	0.89 (0.26–3.03)
1960–1969	4	2.12 (0.71–6.32)	0	0.00 (–)	12	1.18 (0.60–2.33)	5	1.38 (0.51–3.76)	2	0.72 (0.17–3.08)
1970–1979	3	1.21 (0.36–4.10)	7	1.94 (0.82–4.57)	6	0.66 (0.27–1.60)	5	1.34 (0.50–3.60)	4	1.38 (0.47–4.06)
1980+	5	2.05 (0.76–5.55)	8	2.50 (1.10–5.64)	16	1.84 (1.00–3.40)	6	1.75 (0.70–4.40)	8	3.07 (1.37–6.88)
Time since first use (years)[b]										
≤25	5	1.79 (0.67–4.82)	7	1.93 (0.83–4.52)	16	1.65 (0.90–3.00)	6	1.58 (0.63–3.93)	8	2.73 (1.22–6.07)
26–<38	5	1.89 (0.71–5.06)	8	2.09 (0.93–4.69)	11	1.05 (0.53–2.10)	8	1.80 (0.79–4.08)	5	1.51 (0.57–4.00)
38–<45	3	2.14 (0.61–7.47)	0	0.00 (–)	7	0.75 (0.33–1.75)	4	1.45 (0.48–4.38)	1	0.41 (0.05–3.07)
45+	2	1.46 (0.33–6.49)	2	1.22 (0.28–5.38)	6	0.56 (0.23–1.37)	3	1.19 (0.34–4.19)	3	1.02 (0.30–3.52)

[a] Adjusted for age, calendar year of diagnosis/reference date, county of residence, number of full term births, and duration of hormonal contraception

[b] Use defined as regular use after bathing for at least 1 year

[c] Not included are 6 endometrioid borderline, 5 other borderline, and 23 mucinous invasive tumors

≥15 years of age were slightly stronger (e.g., ORs among such women = 1.30 [95% CI: 0.99–1.71] and 1.63 [95% CI: 1.07–2.49], for all ovarian tumors combined and for borderline tumors, respectively).

Risk of mucinous borderline tumors was particularly elevated among women who reported any regular use of perineal dusting powder (OR = 1.78, 95% CI: 0.98–3.23), with a lesser risk increase for serous borderline tumors (Table 3). We observed no association of perineal powder use with risk of serous invasive tumors (OR = 1.01, 95% CI: 0.69–1.47), and some suggestion that risk was elevated for the combined group of endometrioid and clear cell invasive tumors (OR = 1.53, 95% CI: 0.91–2.57). Similar to the overall results, we observed no association with measures of extent of the use of perineal dusting powder for any specific histologic subtype. Elevations in risk noted in our overall results among women in the most recent category of age at or time since first use and in the most recent (1980 or later) calendar period of initiation of powder use were broadly similar across histologic subtypes.

Discussion

A number of case–control studies of ovarian cancer, in addition to ours, have examined the issue of genital powder exposure as a potential risk factor. The validity of all of these studies, including ours, may be influenced by the level of non-response among cases and controls, and by the potential for misclassification (differential and non-differential) of exposure status. The latter derives not just from errors in the recall of the use of genital powder, but from the fact that the presence or concentration of talc can vary

from brand to brand and even within one brand of powder over time. Therefore, even when respondents are asked specifically about perineal exposure to powders that contain talc (as in our study), they may be unable to provide accurate information. Reporting of the use of pure cornstarch powder, however, was quite uncommon in this study; if this information is accurate (and this pattern of use extends to other populations), and if the presence, rather than concentration, of talc in dusting powder is the primary determinant of meaningful exposure, then measures of genital powder use of any type may yet serve as a reasonable surrogate for talc exposure.

In support of an inference that genital exposure to powders has the capacity to cause ovarian cancer is the observation of a 30–60% increase in risk across most case–control studies [3]; in this regard, our findings are similar to prior studies. However, a non-causal interpretation may be consistent with the absence of an overall association in the one cohort study of the question [6], along with the absence in most studies (including the current study) of a trend of increasing risk with increasing duration of exposure [3]. However, ovarian talc particle burden has been found not to correlate with the reported number of lifetime applications [10], which (if not reflective of inaccurate reporting) may indicate that duration of the powder use is not relevant when assessing risk associated with differing levels of exposure to talc.

While the increased risk that we observed was largely restricted to borderline tumors, some studies have reported results either similar to [e.g., 11] or different from [e.g., 5, 12] these latter findings. Also, our results add further inconsistency to the results regarding the strength of association of the perineal powder use with histologic subtypes of disease. In particular, we noted no increase in risk of serous invasive disease, in contrast to some [e.g., 4–6] studies—including the single cohort study [6]—that reported the strongest associations with that subtype. Analyses aimed at examining perineal powder during specific time intervals—whether by calendar year, recency of use, or life intervals in which constituents of perineal powder might ascend through the reproductive tract unimpeded by, e.g., closure of the fallopian tubes—either failed to sharpen exposure–disease relationships or yielded results opposite to those that had been observed or hypothesized by others. For example, Wu et al. [5] observed higher risks among women who initiated talc use before 1975, consistent with the hypothesis that products in use before that year were more likely to be carcinogenic owing to contamination with asbestos fibers; in contrast, we noted stronger associations among women who had only used perineal powder during or after 1980.

It is not evident how (or if) additional investigation will be able to resolve the issue of whether perineal exposure to talc predisposes to ovarian malignancy. Further case–control studies will continue to be hindered by the limitations mentioned above. Data from additional cohort studies would be welcome, but without details concerning the composition of the powders used by cohort members—details that many participants may not be able to provide—the results of such studies may similarly be ambiguous in their interpretation.

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Perineal Talc Exposure and Risk of Ovarian Carcinoma

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BACKGROUND. Clinical and epidemiologic studies have indicated the possible existence of an association between ovarian carcinoma and talcum powder use. Talc particles have been detected in histologic sections of ovarian carcinomas. It has also been demonstrated that inert particles travel from the perineum to the ovaries. Results from epidemiologic investigations have varied, from risks increased by twofold to no significant risk detected.

METHODS. A total of 450 patients with borderline and invasive ovarian carcinoma and 564 population controls in metropolitan Toronto and nearby areas of southern Ontario, Canada, were identified. These subjects were interviewed about their reproductive and menstrual histories as well as their exposure to dusting powders. Continuous unconditional logistic regression methods were used for analysis.

RESULTS. Exposure to talc, via sanitary napkins, direct application to the perineum, or both, was significantly associated with risk of ovarian carcinoma (odds ratio [OR] 1.42, 95% confidence interval [CI] 1.08–1.86). A borderline-significant association was detected between duration of talc exposure and risk (OR 1.09, 95% CI 0.98–1.21, per 10 years of exposure). No significant association was found between frequency of exposure and risk. In comparing invasive and borderline carcinomas, risk remained elevated for both carcinoma types. Only risk for invasive carcinoma was statistically significant.

CONCLUSIONS. This investigation supports previous contentions that exposure to talc may increase risk of ovarian carcinoma. Questionable trends in duration and frequency of exposure suggest that further studies may be needed to clarify the role of talc in the etiology of this disease. ***Cancer*** **1997;79:2396–401.**

KEYWORDS: case-control studies, ovarian neoplasms, risk factors, talc.

Ovarian carcinoma is the most commonly fatal gynecologic malignancy.[1] In the United States, approximately 26,000 women develop the disease annually. Overall, the lifetime risk for the development of ovarian carcinoma is 1.4 in 100.[2] Because industrialized nations generally have higher prevalence rates of this disease, environmental exposure has been suggested as an etiologic factor.[1]

Asbestos, a known sclerosing agent, has been shown to cause bronchogenic lung carcinoma and mesothelioma.[3] The incidence of ovarian carcinoma generally increases with greater incidence of asbestosis.[4] Furthermore, female asbestos workers have unusually high numbers of peritoneal neoplasms, and an association between ovarian carcinoma and asbestos exposure has also been observed in animal models.[2,5] Due to its chemical similarity to asbestos, talc has long been suspected as a lung and ovarian carcinogen.[2,6] Like asbestos, talc is a magnesium silicate. Pulverized talc, or talcum powder, is a popular bath and cosmetic product because of its absorbent and

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water-repellent properties. Talcum powder is often applied to sanitary napkins and condoms, as well as directly to the perineum, typically after bathing. Early pathology studies have identified talc particles in ovarian tumors.[7,8] An extraction-replication technique developed by Henderson et al.[7] detected talc particles in approximately 75% of ovarian tumors examined. Furthermore, studies of the transport of particles in the human female reproductive tract have shown that nonmotile, inert carbon particles deposited in the vagina can be recovered 30–35 minutes later in the fallopian tubes.[9] Although findings of talc particles in ovarian tumors initially met with skepticism, subsequent evaluations appeared to support the contention of an association between talc exposure and ovarian carcinoma.[10]

In addition to pathologic and clinical studies, several epidemiologic studies have addressed the plausibility of an association between talc and ovarian carcinoma. Although many of these case-control studies revealed elevated risks,[11–18] risk estimates from other studies were not statistically significant[19–20] or were about unity.[21] Thus, the possibility of a risk of ovarian carcinoma that is related to talc exposure remains to be investigated further. The population-based case-control analysis described in this article was conducted to examine the role of talc in ovarian carcinoma, with consideration of the duration, frequency, and method of exposure.

MATERIALS AND METHODS

Study methods have been reported in detail elsewhere[22] and will be summarized here. Our study population consisted of women between the ages of 35 and 79 years residing in the highly populated area surrounding the western end of Lake Ontario, Canada. Cases were women who had histologically confirmed primary, invasive or borderline epithelial ovarian tumors first diagnosed between November 1, 1989, and October 31, 1992. Of the 631 women identified as cases, 450 (71.3%) were interviewed. Fifty-five (8.7%) had died, but proxy interviews were not conducted; 29 (4.6%) had physicians who refused consent; 30 (4.8%) were too ill to participate; 17 (2.7%) were lost to follow-up; and 50 (7.9%) refused to participate.

Population-based controls were identified through the Ontario Ministry of Finance. Information on name, address, age, and gender was obtained from the Enumeration Composite Record listings, which include all homeowners, tenants, and family members, i.e., all persons in the province. From this listing, women living in the study area during the same 3-year period as the cases were randomly selected. Controls were matched to the cases within 3 15-year age groups. Initial contact by letter was followed up with phone calls to determine eligibility. Women with bilateral oophorectomy performed at least 1 year previously were excluded. Overall, 873 eligible controls were identified. Of these women, 564 (64.5%) were interviewed. The remainder either refused to participate (30.2%), were too ill to participate (1.9%), or were lost to follow-up (3.2%).

A questionnaire was developed to detail the medical and reproductive histories of the subjects. This questionnaire was administered during an in-person, in-home interview after informed consent was obtained. The questionnaire focused on menstrual characteristics, pregnancies, and hormone and contraceptive use. Questions about regular talc use and type of talc use, as well as questions from which information about duration and frequency of exposure could be derived, were included. Dusting or powdering behaviors considered included regular application of talc to the perineum after showering or bathing and dusting of talc on sanitary napkins. Parallel information about cornstarch use was also obtained.

Analysis was performed by modeling the data through multiple unconditional logistic regression with the SAS statistical package. In addition to the variables of interest examined here, the models included indicator terms for the age categories of the frequency matching (35–49, 50–64, and 65–79 years), and age as a continuous variable was also included to adjust for residual age effects. Models also contained terms for total years of oral contraceptive use; number of full-term pregnancies; average duration of breastfeeding per pregnancy; and ever having had a tubal ligation, a hysterectomy, or a mother or sister with ovarian or breast carcinoma.

RESULTS

Table 1 shows the descriptive characteristics of the 450 ovarian carcinoma cases and the 564 population controls. Age at interview was used as a matching variable. As observed in many reports,[20,22,23] controls had, on average, a greater number of full-term pregnancies. A higher percentage of controls had had a tubal ligation or a hysterectomy, whereas a higher percentage of cases had a mother or sister with ovarian or breast carcinoma. Years of oral contraceptive use and months of lactation per pregnancy showed trends of decreasing risk with increasing exposure. There were no appreciable differences in the characteristics shown in Table 1 between controls who reported ever having used talc and those not reporting talc use.

Table 2 gives the associations between dusting behaviors and risk of ovarian carcinoma. Overall, 44.0% of cases and 35.6% of controls reported exposure to

TABLE 1
Descriptive Characteristics of Study Population

Characteristics	Cases	Controls	Adjusted[a] OR	(95% CI)
Age at interview (yrs)	57.2	57.5	Matched	
Born in Canada or the U.S. (%)	59.1	64.7	0.843	(0.64–1.11)
Race (% black)	1.56	1.95	0.804	(0.30–2.17)
Length of schooling (yrs)	12.3	12.5	0.983	(0.95–1.02)
Number of full-term pregnancies	1.90	2.45	0.820[b]	(0.71–0.92)
Yrs of oral contraceptive use	4.17	5.53	0.915[b]	(0.88–0.95)
Mos of lactation per pregnancy	3.95	4.21	0.946[b]	(0.91–0.99)
Ever had tubal ligation (%)	18.0	24.3	0.659	(0.47–0.93)
Ever had hysterectomy (%)	13.8	24.8	0.485	(0.34–0.69)
Mother/sister with breast or ovarian carcinoma (%)	12.9	7.98	1.917	(1.24–2.97)

OR: odds ratio; CI: confidence interval.
[a] Adjusted for age at interview; yrs of oral contraceptive use; number of full-term pregnancies; average duration of breastfeeding per pregnancy; and ever having had a tubal ligation, hysterectomy, or a mother or sister with ovarian or breast carcinoma.
[b] OR per each, yr or mo, respectively.

talc. Women with any regular talc exposure were at an increased risk (odds ratio [OR] 1.42, 95% confidence interval [CI] 1.08–1.86). The use of cornstarch, or cornstarch sometimes and talc sometimes, did not yield a significant association with risk (cornstarch OR 0.31, 95% CI 0.06–1.66; cornstarch/talc OR 0.68, 95% CI 0.18–2.55). However, application of cornstarch to sanitary napkins or directly to the perineum was not common in this population; less than 2% of the study population reported this behavior. With respect to the type of exposure, substantially more women reported applying talc to their bodies after bathing or showering than using talc on their sanitary napkins. Some 11.3% of cases and 8.7% of controls reported using talc on sanitary napkins. A nonsignificant increase in odds was observed for talc exposure via sanitary napkins (OR 1.26, 95% CI 0.81–1.96). In total, 38.2% of cases and 32.4% of controls reported that they had, at some time, regularly used talc after bathing or showering. The odds ratio seen for use of talc after bathing or showering alone was of borderline statistical significance (OR 1.31, 95% CI 1.00–1.73).

The association between duration and frequency of talc use and ovarian carcinoma was also examined. The mean years of after-bath talc use were 32.9 for cases who had ever used talc after bathing and 35.4 for controls. A borderline-significant trend for years of talc exposure and risk of ovarian carcinoma was found (OR per 10 years of use 1.06, 95% CI 0.99–1.14). When duration was considered categorized by tertiles of control use, only durations of less than 30 years of talc use showed increased risk, relative to no talc exposure. The mean frequency of talc use among those who had ever used it was 14.6 applications per month for cases; for controls, it was 17.2 applications per month. As a continuous variable, monthly frequency did not significantly increase risk of ovarian carcinoma. Categoric analysis of frequency showed that frequencies of less than 10 applications per month may be associated with increased risk; greater frequencies, however, did not show significant increases in risk.

To examine the effects of calendar time of exposure and of hysterectomy or tubal ligation, we assumed that regular after-bath talc use commenced at age 20 years. Table 2 shows that duration of after-bath talc use both before and after 1970 appeared to be associated with risk of ovarian carcinoma. As might be expected, the increased risk seemed to be related mostly to talc use prior to tubal ligation or hysterectomy (Table 2). There were no differences in these results when various starting ages between 15 and 25 years were considered.

The association between talc exposure and invasive ovarian carcinoma, as compared with borderline ovarian carcinoma, was also examined (Table 3). Although the risk remained elevated for both carcinoma types, only the risk for invasive carcinoma was statistically significant. No differences in risk with respect to serous, mucinous, or endometrioid tumors were observed in our data.

Substantial alteration in risk of ovarian carcinoma was not observed for general sanitary napkin use com-

TABLE 2
Risk of Ovarian Carcinoma with Use of Talcum Powder or Cornstarch

	No. (%)				Adjusted[b]	
	Cases	Controls	Case mean[a]	Control mean[a]	OR	(95% CI)
Any talc exposure	198 (44.0)	201 (35.6)			1.420	(1.08–1.86)
Any cornstarch	2 (0.44)	5 (0.85)			0.305	(0.06–1.66)
Cornstarch/talc	4 (0.89)	7 (1.24)			0.681	(0.18–2.55)
Type of talc exposure						
Sanitary napkin	51 (11.3)	49 (8.69)			1.262	(0.81–1.96)
After bathing	172 (38.2)	183 (32.4)			1.312	(1.00–1.73)
After-bath talc use/mo			14.6	17.2	0.890[c]	(0.74–1.07)
<10	76 (16.9)	59 (10.5)			1.836	(1.24–2.73)
10–25	54 (12.0)	64 (11.3)			1.128	(0.74–1.72)
>25	41 (9.11)	60 (10.6)			0.951	(0.61–1.49)
Yrs of after-bath talc use			32.9	35.4	1.091[c]	(0.98–1.21)
<30	60 (13.3)	52 (9.22)			1.697	(1.09–2.64)
30–40	71 (15.8)	67 (11.9)			1.435	(0.96–2.15)
>40	41 (9.11)	64 (11.3)			0.865	(0.54–1.38)
Yrs of after-bath talc use						
Before 1970			26.4	24.9	1.090[c]	(0.98–1.22)
After 1970			6.5	10.4	1.095[c]	(0.89–1.35)
Yrs of after-bath talc use						
Before tubal ligation/hysterectomy			28.4	26.9	1.105[c]	(0.99–1.24)
After tubal ligation/hysterectomy			4.5	8.5	1.031[c]	(0.82–1.29)

OR: odds ratio; CI: confidence interval.
[a] Mean among those who had ever used talc.
[b] Adjusted as in Table 1.
[c] OR for the continuous variable, shown per 10 applications per mo or 10 yrs of use, as appropriate.

TABLE 3
Risk of Ovarian Carcinoma for Women Who Ever Used Talcum Powder Regularly, by Case Histology

Histologic type	Total no. of cases	No. (%) who used talcum powder	Adjusted[a] OR	Adjusted[a] (95% CI)
Invasive	367	166 (45.2)	1.513	(1.13–2.02)
Borderline	83	32 (38.6)	1.237	(0.76–2.02)
Serous	254	109 (42.9)	1.336	(0.96–1.85)
Mucinous	80	35 (43.8)	1.585	(0.97–2.58)
Endometrioid	74	36 (48.6)	1.671	(1.00–2.79)

OR: odds ratio; CI: confidence interval.
[a] Adjusted as in Table 1.

pared with tampon use. Because few women used sanitary napkins or tampons exclusively, the risk was examined as a percentage of the length of time that sanitary napkins were used and a percentage of the length of time that tampons were used. Significant trends in risk were not detected for a 10% difference in napkin use (OR 1.06, 95% CI 0.99–1.13) or for a 10% increase in tampon use (OR 0.99, 95% CI 0.93–1.05).

DISCUSSION

Results from experimental and epidemiologic studies conducted thus far indicate a possible association between talc exposure and ovarian carcinoma. Histologic evidence first indicated that contaminants such talc may become embedded in ovarian tumors.[8,24] Experimental studies have shown that external talc exposure may eventually reach the ovaries. Henderson et al.[10] demonstrated that talc was present in ovaries after deposition of a talc suspension in the vagina and cervical os in rats. Similarly, Egli and Newton[9] revealed in human studies that inert carbon particles deposited in the vagina can later be recovered in the fallopian tubes. Although these studies demonstrated a possible route of exposure to talc, they were nevertheless unable to address the effects of long term talc use.

Surprisingly, few subsequent pathologic and clinical studies have been conducted. Epidemiologic studies addressing the possible association between talc and ovarian carcinoma have generally reported increased risk estimates. Cramer et al.[11] found a relative risk of 1.92 (95% CI 1.3–2.9). Rosenblatt et al.[12] reported a relative risk of 2.4 (95% CI 1.1–5.3) for any genital talc exposure. Likewise, Purdie et al. found a

significant positive association between talc and ovarian carcinoma,[14] and other recent studies also support the hypothesis of elevated risk of ovarian carcinoma with talc exposure, reporting risk increases of approximately two-fold.[16–18] A few studies have found only marginally significant or nonsignificant elevations in risk.[19–21] However, in investigations such as that reported by Tzonou et al., the number of women who reported talc usage was low.[21] More detailed discussion of many of those studies may be found in reviews elsewhere.[25,26]

This study sought to elucidate further the relationship between talc and ovarian carcinoma. Talc exposure through direct perineal application and via sanitary napkins, the frequency and duration of exposure, and the effect of talc within specific histologic subtypes were examined. Dusting with talcum powder was common behavior for more than one-third of cases and controls. The primary mode of talc exposure appeared to be direct application to the perineum. Although talc exposure via contraceptives such as condoms and diaphragms has been previously investigated,[27] this type of behavior was rare in the current study population and therefore omitted from analyses. Overall, greater risk was associated with any regular talc exposure (OR 1.42, 95% CI 1.08–1.86). Any talc exposure included talc accumulated from sanitary napkins, from powdering after bathing, or from both behaviors. Talc exposures via sanitary napkin alone or after bathing conveyed similar magnitudes of increased risk.

Commercial talc substitutes often replace talc with cornstarch. Furthermore, women may choose to powder or dust with cornstarch instead of talc. When cornstarch was assessed in relation to risk of ovarian carcinoma, no associations were found. This suggests that the association between talc use and risk of ovarian carcinoma may not be due simply to a difference in focus on hygiene between cases and controls. Use of cornstarch, however, was rare in our population, as less than 1% of the cases and controls reported use of cornstarch alone, and very few cases and controls reported use of cornstarch sometimes and talc sometimes.

A questionable dose-response relationship was observed between duration or frequency of exposure and risk. Duration as a continuous variable indicated that risk may increase with increasing years of talc exposure. These results are similar to findings by Cramer et al.,[11] Harlow et al.,[13] Harlow and Weiss,[28] Cook et al.,[18] and Whittemore et al.,[19] in which trends of duration and frequency were not significant. Booth et al.[23] reported a marginally significant trend with frequency. It is noteworthy that exposures of less than 30 years, at frequencies of less than 10 applications per month, and prior to tubal ligation or hysterectomy showed the most significant elevations in risk in the current study.

When the outcome, ovarian carcinoma, was further segregated into invasive and borderline carcinomas, talc exposure was associated with both but was only significant for invasive carcinomas. This result contrasts with the observations of Harlow et al.,[13] who found the strongest talc–ovarian carcinoma associations among women with endometrioid and borderline tumors. Cook et al.[18] reported no increase in risk of mucinous tumors; this was similar to our observation that mucinous tumors may not be associated with other ovarian carcinoma risk factors.[29] An earlier study, however, found no variation in risk by histologic subtype,[11] and the current study also found no differences in talc use associated with serous, mucinous, or endometrioid tumors.

Several lines of evidence support the argument for an association between talc usage and ovarian carcinoma. Talc and asbestos are chemically related; and although asbestos contamination in talc products has been closely regulated, talc and asbestos are frequently found together in mining strata. Asbestos is a known cause of pleural and peritoneal mesotheliomas, which are histologically similar to ovarian carcinomas.[19] Two possible mechanisms have been suggested for the role of talc in the etiology of ovarian carcinoma. With ovulation, entrapment of the ovarian epithelium within the stroma occurs. During this time, talc, if present, may become incorporated into these inclusion cysts, providing a favorable environment for carcinogenesis.[11] Alternatively, talc may serve to stimulate the entrapment of the surface epithelium and may act in a manner similar to "incessant ovulation," which has been proposed as an etiologic factor in ovarian carcinoma.[11,30]

Differences in talc concentration among various baby powders, body powders, and deodorizing powders were not investigated in this study. Furthermore, reporting error in reported talc use and failure to interview all eligible case and control subjects may also have led to biases. As with any case-control study, the possibility of selection bias and information bias exists, although the consistency of this study with others that have addressed reproductive factors and ovarian carcinoma is reassuring.[23] Further discussion of the strengths and weaknesses of the current study may be found in a previous report.[23]

The results of this study appear to support the contention that talc exposure increases risk of ovarian carcinoma. Dusting with talcum powder is not an unusual practice for women, and, given the heterogeneity

of the etiology and course of ovarian carcinoma, any possible harmful practices, particularly those with little benefit, should be deliberated. It should be emphasized, however, that further studies are needed to clarify the role of talc in the etiology of ovarian carcinoma.

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